No. 17-1229

In the Supreme Court of the United States

HELSINN HEALTHCARE S.A., PETITIONER

v.

TEVA PHARMACEUTICALS USA, INC.,
AND TEVA PHARMACEUTICAL INDUSTRIES, LTD.

ON WRIT OF CERTIORARI
TO THE UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

JOINT APPENDIX

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PETITION FOR A WRIT OF CERTIORARI FILED: FEBRUARY 28, 2018
CERTIORARI GRANTED: JUNE 25, 2018

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The following opinions, decisions, judgments, and orders have been omitted in printing the joint appendix because they appear as appendices to the petition for certiorari and the brief in opposition to the petition for certiorari as follows:

Br. in Opp. App. 1a:	Court of appeals order denying motion to stay mandate, Jan. 22, 2018
Pet. App. 1a:	Court of appeals order denying rehearing, Jan. 16, 2018
Pet. App. 17a:	Court of appeals opinion, May 1, 2017
Pet. App. 53a:	District court supplemental opinion, Mar. 3, 2016
Pet. App. 232a:	District court final judgment, Nov. 16, 2015
Pet. App. 235a:	District court memorandum opinion, Nov. 13, 2015

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

No. 16-1284

HELSINN HEALTHCARE S.A.,
Plaintiff-Appellee,

v.

TEVA PHARMACEUTICALS USA, INC.,
TEVA PHARMACEUTICAL INDUSTRIES, LTD.,
Defendants-Appellants.

DOCKET ENTRIES

DATE	NO.	PROCEEDINGS
12/04/2015	1	Appeal docketed. Received: 12/03/2015. [293675] Entry of Appearance due 12/18/2015. Certificate of Interest is due on 12/18/2015. Docketing Statement due 12/18/2015. Appellant/Petitioner's brief is due 02/02/2016. [JCA] [Entered: 12/04/2015 01:12 PM]
* * * * *		
03/08/216	39	CORRECTED BRIEF FILED for Appellants Teva Pharmaceutical Industries, Ltd. and Teva Pharmaceuticals USA, Inc. [38]. Number of

DATE	NO.	PROCEEDINGS
		Pages: 62. Service: 03/08/2016 by email. Pursuant to ECF-10, filer is directed to file six copies of the brief in paper format. The paper copies of the brief should be received by the court on or before 03/14/2016. Appellees Helsinn Healthcare S.A. and Roche Palo Alto LLC brief is due 04/21/2016. [316820] [JCA] [Entered: 03/08/2016 03:50 PM]
		* * * * *
03/14/2016	43	AMICUS BRIEF FILED for 42 Intellectual Property Professors [42]. Number of Pages: 22. Service: 03/14/2016 by email. Pursuant to ECF-10, filer is directed to file six copies of the brief in paper format. The paper copies of the brief should be received by the court on or before 03/21/2016. [318603] [JCA] [Entered: 03/15/2016 09:34 AM]
		* * * * *
03/15/2016	47	AMICUS BRIEF FILED for Ron D. Katznelson, Ph.D. [46]. Number of Pages: 27. Service: 03/15/2016 by clerk. [318912] [JCA] [Entered: 03/15/2016 04:11 PM]
		* * * * *
10/28/2015	59	AMICUS BRIEF FILED for Lamar Smith [56]. Number of Pages: 34. Service: 04/21/2016 by email.

DATE	NO.	PROCEEDINGS
		Pursuant to Fed. Cir. R. 29(a), filer is directed to file six copies of the brief in paper format. The paper copies of the brief should be received by the court on or before 04/27/2016. [328738] [JCA] [Entered: 04/22/2016 10:08 AM]
		* * * * *
04/25/2016	64	BRIEF FILED for Appellees Helsinn Healthcare S.A. and Roche Palo Alto LLC [62]. Number of Pages: 60. Service: 04/25/2016 by email. Pursuant to Fed. Cir. R. 31(b), filer is directed to file six copies of the brief in paper format. The paper copies of the brief should be received by the court on or before 05/02/2016. Appellants' reply brief due 5/13/2016. [329553] [MJL] [Entered: 04/26/2016 09:37 AM]
		* * * * *
04/27/2016	74	AMICUS BRIEF FILED for The Naples Roundtable, Inc. [67]. Number of Pages: 17. Service: 04/27/2016 by email. Pursuant to Fed. Cir. R. 29(a), filer is directed to file six copies of the brief in paper format. The paper copies of the brief should be received by the court on or before 05/02/2016.

DATE	NO.	PROCEEDINGS
		[330068] [JCA] [Entered: 04/27/2016 03:20 PM]
05/02/2016	90	AMICUS BRIEF FILED for US [86]. Number of Pages: 25. Service: 05/02/2016 by email. Pursuant to Fed. Cir. R. 29(a), filer is directed to file six copies of the brief in paper format. The paper copies of the brief should be received by the court on or before 05/09/2016. [331554] [JCA] [Entered: 05/03/2016 11:12 AM]
		* * * * *
05/02/2016	93	AMICUS BRIEF FILED for AIPLA [85]. Number of Pages: 26. Service: 05/02/2016 by email. Pursuant to Fed. Cir. R. 29(a), filer is directed to file six copies of the brief in paper format. The paper copies of the brief should be received by the court on or before 05/09/2016. [331603] [JCA] [Entered: 05/03/2016 12:10 PM]
05/02/2016	97	AMICUS BRIEF FILED for Biotechnology Innovation Organization and Pharmaceutical Research and Manufacturers of America [89]. Number of Pages: 27. Service: 05/02/2016 by email. Pursuant to Fed. Cir. R. 29(a), filer is directed to file six copies of the brief in paper format. The paper copies of the

DATE	NO.	PROCEEDINGS
		brief should be received by the court on or before 05/09/2016. [331621] [JCA] [Entered: 05/03/2016 12:33 PM]
		* * * * *
05/13/2016	109	REPLY BRIEF FILED for Appellants Teva Pharmaceutical Industries, Ltd. and Teva Pharmaceuticals USA, Inc. [108]. Number of Pages: 31. Service: 05/13/2016 by email. Pursuant to Fed. Cir. R. 31(b), filer is directed to file six copies of the brief in paper format. The paper copies of the brief should be received by the court on or before 05/23/2016. Appendix is due 05/23/2016. [335157] [JCA] [Entered: 05/16/2016 09:53 AM]
		* * * * *
05/23/2016	115	APPENDIX FILED for Teva Pharmaceutical Industries, Ltd. and Teva Pharmaceuticals USA, Inc. [114]. Number of Pages: 624. Service: 05/23/2016 by email. Pursuant to Fed. Cir. R. 30(a)(5), filer is directed to file six copies of the appendix in paper format. The paper copies should be received by the court on or before 05/31/2016. [337793] [MJL] [Entered: 05/24/2016 09:40 AM]

DATE	NO.	PROCEEDINGS
		* * * * *
07/13/2016	123	Citation of Supplemental Authority pursuant to Fed. R. App. P. 28(j) for Appellants Teva Pharmaceutical Industries, Ltd. and Teva Pharmaceuticals USA, Inc. Service: 07/13/2016 by email, US mail. [350548] [Andrew Nichols] [Entered: 07/13/2016 03:01 PM]
07/14/2016	124	Citation of Supplemental Authority pursuant to Fed. R. App. P. 28(j) for Appellee Helsinn Healthcare S.A. Service: 07/14/2016 by email. [350741] [Joseph O'Malley] [Entered: 07/14/2016 11:15 AM]
		* * * * *
10/04/2016	131	Submitted after ORAL ARGUMENT by Mr. William Ernest Havemann for US, Mr. George C. Lombardi, Esq. for Teva Pharmaceutical Industries, Ltd. and Teva Pharmaceuticals USA, Inc. and Mr. Joseph M. O'Malley, Jr. for Helsinn Healthcare S.A. Panel: Judge: Dyk, Judge: Mayer, Judge: O'Malley. [371295] [JCP] [Entered: 10/04/2016 11:55 AM]
10/17/2016	132	Citation of Supplemental Authority pursuant to Fed. R. App. P. 28(j) for Appellee Helsinn Healthcare S.A. Service: 10/17/2016 by email, US

DATE	NO.	PROCEEDINGS
		mail. [374729] [Joseph O'Malley] [Entered: 10/17/2016 11:01 AM]
05/01/2017	133	OPINION and JUDGMENT filed. The judgment or decision is: Reversed. (Precedential Opinion). (For the Court: Dyk, Circuit Judge; Mayer, Circuit Judge and O'Malley, Circuit Judge). [428102] [16-1284, 16-1787] [JCA] [Entered: 05/01/2017 09:42 AM]
		* * * * *
06/30/2017	136	Petition for en banc rehearing filed by Appellee Helsinn Healthcare S.A. Service: 06/30/2017 by email, US mail. *The paper copies of the petition must be filed within two business days (see Fed. Cir. R. 35(c)(4).The required paper copies should be received by the court on or before 07/05/2017 [443615] [Joseph O'Malley] [Entered: 06/30/2017 03:57 PM]*
		* * * * *
07/11/2017	151	AMICUS BRIEF FILED on Petition for Lamar Smith [137]. Pages: 10. The filer is directed to submit the appropriate number of copies within two days, see Fed. Cir. R. 25(c). [445587] [SMJ] [Entered: 07/11/2017 12:01 PM]

DATE	NO.	PROCEEDINGS
		* * * * *
07/14/2017	157	AMICUS BRIEF FILED on Petition for Intellectual Property Owners Association [149]. Pages: 11. The filer is directed to submit the appropriate number of copies within two days, see Fed. Cir. R. 25(c). [446568] [SMJ] [Entered: 07/14/2017 10:53 AM]
		* * * * *
07/19/2017	177	AMICUS BRIEF FILED on Petition for AIPLA [156]. Pages: 10. The filer is directed to submit the appropriate number of copies within two days, see Fed. Cir. R. 25(c). [447619] [SMJ] [Entered: 07/19/2017 01:00 PM]
07/19/2017	178	AMICUS BRIEF FILED on Petition for Biotechnology Innovation Organization [160]. Pages: 10. The filer is directed to submit the appropriate number of copies within two days, see Fed. Cir. R. 25(c). [447621] [SMJ] [Entered: 07/19/2017 01:02 PM]
07/19/2017	179	AMICUS BRIEF FILED on Petition for Boston Patent Law Association [166]. Pages: 9. The filer is directed to submit the appropriate number of copies within two days, see Fed. Cir. R. 25(c). [447624]

DATE	NO.	PROCEEDINGS
		[SMJ] [Entered: 07/19/2017 01:10 PM]
07/19/2017	180	AMICUS BRIEF FILED on Petition for Pharmaceutical Research and Manufacturers of America [173]. Pages: 10. The filer is directed to submit the appropriate number of copies within two days, see Fed. Cir. R. 25(c). [447626] [SMJ] [Entered: 07/19/2017 01:15 PM]
* * * * *		
08/25/2017	193	RESPONSE of Appellants Teva Pharmaceutical Industries, Ltd. and Teva Pharmaceuticals USA, Inc. to the petition for en banc rehearing [136] filed by Appellee Helsinn Healthcare S.A. in 16-1284. Service: 08/25/2017 by email, US mail. [456705] [Julia Johnson] [Entered: 08/25/2017 01:39 PM]
* * * * *		
01/16/2018	195	ORDER filed denying [136] petition for en banc rehearing filed by Helsinn Healthcare S.A. By: En Banc (Per Curiam). O'Malley, Circuit Judge, concurring in the denial of panel rehearing. Service as of this date by Clerk of Court. [489762] [SMJ] [Entered: 01/16/2018 02:01 PM]

DATE	NO.	PROCEEDINGS
		* * * * *
01/18/2018	199	MOTION of Appellee Helsinn Healthcare S.A. to stay execution of the mandate until Pending Petition for Writ of Certiorari. [Consent: opposed]. Service: 01/18/2018 by email, US mail. [490654] [Joseph O'Malley] [Entered: 01/18/2018 11:50 AM]
		* * * * *
01/22/2018	210	RESPONSE of Appellants Teva Pharmaceutical Industries, Ltd. and Teva Pharmaceuticals USA, Inc. to the motion to stay mandate [199] filed by Appellee Helsinn Healthcare S.A. in 16-1284. Service: 01/22/2018 by email, US mail. [491404] [Steffen Johnson] [Entered: 01/22/2018 12:42 PM]
		* * * * *
01/22/2018	212	ORDER filed denying [199] motion to stay mandate filed by Helsinn Healthcare S.A. By: Merits Panel (Per Curiam). Service as of this date by Clerk of Court. [491632] [SMJ] [Entered: 01/22/2018 04:59 PM]
		* * * * *

DATE	NO.	PROCEEDINGS
01/29/2018	215	Mandate issued to the United States District Court for the District of New Jersey. Service as of this date by Clerk of Court. [493476] [16-1284, 16-1787] [SMJ] [Entered: 01/29/2018 04:32 PM]
03/05/2018	216	Petition for writ of Certiorari filed on 02/28/2018, and placed on the docket 03/02/2018, in the Supreme Court of the United States. Supreme Court #: 17-1229, Helsinn Healthcare S.A. v. Teva Pharmaceuticals USA, Inc., et al. [502582] [JAB] [Entered: 03/05/2018 02:54 PM]

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

No. 2:11-cv-03962-SRC-CLW

HELSINN HEALTHCARE S.A.,
Plaintiff,

v.

TEVA PHARMACEUTICALS USA, INC., and
TEVA PHARMACEUTICAL INDUSTRIES, LTD.,
Defendants.

DOCKET ENTRIES

DATE	NO.	PROCEEDINGS
07/08/2011	1	COMPLAINT against DR. REDDY'S LABORATORIES, INC., DR. REDDY'S LABORATORIES, LTD., SANDOZ INC., TEVA PHARMACEUTICAL INDUSTRIES, LTD., TEVA PHARMACEUTICALS USA, INC. (Filing fee $ 350 receipt number 3820157.) NO JURY DEMAND., filed by HELSINN HEALTHCARE S.A., ROCHE PALO ALTO LLC. (Attachments: # 1 Exhibit A, # 2 Exhibit B, # 3 Civil Cover Sheet) (ma) (Entered: 07/11/2011)

DATE	NO.	PROCEEDINGS
		* * * * *
08/31/2011	33	ANSWER to Complaint, COUNTERCLAIM against All Plaintiffs by DR. REDDY'S LABORATORIES, INC., DR. REDDY'S LABORATORIES, LTD. (Attachments: # 1 Certificate of Service) (IMBACUAN, MICHAEL) (Entered: 08/31/2011)
		* * * * *
09/13/2011	38	ANSWER to Complaint *For Patent Infringement*, COUNTERCLAIM against HELSINN HEALTHCARE S.A., ROCHE PALO ALTO LLC by SANDOZ INC. (WIGGINS, SHEILA) (Entered: 09/13/2011)
09/13/2011	39	ANSWER to Complaint *and Affirmative Defenses* by TEVA PHARMACEUTICAL INDUSTRIES, LTD., TEVA PHARMACEUTICALS USA, INC. (PATUNAS, MICHAEL) (Entered: 09/13/2011)
		* * * * *
10/05/2011	60	ANSWER to Counterclaim *of Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc.* by HELSINN HEALTHCARE S.A., ROCHE PALO ALTO LLC. (At-

DATE	NO.	PROCEEDINGS
		tachments: # 1 Certificate of Service) (LIZZA, CHARLES) (Entered: 10/05/2011)
		* * * * *
10/21/2011	67	ANSWER to Counterclaim *of Sandoz Inc.* by HELSINN HEALTHCARE S.A., ROCHE PALO ALTO LLC. (Attachments: # 1 Certificate of Service) (LIZZA, CHARLES) (Entered: 10/21/2011)
		* * * * *
12/05/2011	77	ANSWER to Complaint by TEVA PHARMACEUTICAL INDUSTRIES, LTD., TEVA PHARMACEUTICALS USA, INC. (PATUNAS, MICHAEL) (Entered: 12/05/2011)
		* * * * *
04/05/2012	85	STATEMENT *Joint Claim Construction and Prehearing Statement* by HELSINN HEALTHCARE S.A., ROCHE PALO ALTO LLC. (Attachments: # 1 Certificate of Service) (LIZZA, CHARLES) (Entered: 04/05/2012)
		* * * * *

DATE	NO.	PROCEEDINGS
05/21/2012	88	BRIEF *Defendants' Opening Claim Construction Brief* (PATUNAS, MICHAEL) (Entered: 05/21/2012)
		* * * * *
05/21/2012	92	MARKMAN OPENING BRIEF *on behalf of Plaintiffs Helsinn Healthcare S.A. and Roche Palo Alto LLC* (Attachments: # 1 Declaration of A. Ni - Part 1, # 2 Declaration of A. Ni - Part 2, # 3 Certificate of Service) (LIZZA, CHARLES) (Entered: 05/21/2012)
		* * * * *
07/20/2012	94	MARKMAN RESPONSE BRIEF re 92 Markman Opening Brief (Attachments: # 1 Declaration of Julia Johnson) (PATUNAS, MICHAEL) (Entered: 07/20/2012)
		* * * * *
07/20/2012	96	MARKMAN RESPONSE BRIEF re 92 Markman Opening Brief (Attachments: # 1 Declaration of Angela C. Ni, # 2 Certificate of Service) (LIZZA, CHARLES) (Entered: 07/20/2012)
07/20/2012	97	MARKMAN RESPONSE BRIEF re 92 Markman Opening Brief (At-

DATE	NO.	PROCEEDINGS
		tachments: # 1 Declaration of Angela C. Ni) (LIZZA, CHARLES) (Entered: 07/20/2012)
		* * * * *
02/15/2013	124	MOTION to Amend/Correct *Invalidity Contentions* by TEVA PHARMACEUTICAL INDUSTRIES, LTD., TEVA PHARMACEUTICALS USA, INC. (Attachments: # 1 Brief in Support of Motion for Leave to Amend Invalidity Contentions, # 2 Declaration of Mayra V. Tarantino, # 3 Exhibit 1, # 4 Exhibit 2, # 5 Exhibit 4, # 6 Exhibit 5, # 7 Exhibit 6, # 8 Exhibit 7, # 9 Exhibit 10, # 10 Exhibit 11, # 11 Exhibit 12, # 12 Text of Proposed Order) (TARANTINO, MAYRA) (Entered: 02/15/2013)
		* * * * *
03/08/2013	130	MEMORANDUM in Opposition filed by HELSINN HEALTHCARE S.A., ROCHE PALO ALTO LLC re 124 MOTION to Amend/Correct *Invalidity Contentions*, 120 MOTION to Amend/Correct *Motion for Leave to Serve its Second Amended Invalidity Contentions*, 119 MOTION to Amend/Correct *Invalidity Contentions* (Attachments: # 1 Decla-

DATE	NO.	PROCEEDINGS
		ration of E. Dittmann, # 2 Certificate of Service) (LIZZA, CHARLES) (Entered: 03/08/2013)
		* * * * *
03/15/2013	134	REPLY BRIEF to Opposition to Motion filed by TEVA PHARMACEUTICAL INDUSTRIES, LTD., TEVA PHARMACEUTICALS USA, INC. re 124 MOTION to Amend/Correct *Invalidity Contentions* (Attachments: # 1 Declaration of Mayra V. Tarantino, # 2 Exhibit C to Tarantino Declaration, # 3 Exhibit D to Tarantino Declaration, # 4 Exhibit E to Tarantino Declaration) (TARANTINO, MAYRA) (Entered: 03/15/2013)
		* * * * *
06/09/2014	175	STATEMENT *Joint Claim Construction and Prehearing Statement* by HELSINN HEALTHCARE S.A. (Attachments: # 1 Certificate of Service) (LIZZA, CHARLES) (Entered: 06/09/2014)
06/09/2014	176	MARKMAN OPENING BRIEF (Attachments: # 1 Declaration of Brendan F. Baker, # 2 Exhibit 1 to Declaration, # 3 Exhibit 2 to Decla-

DATE	NO.	PROCEEDINGS
		ration, # 4 Exhibit 3 to Declaration) (TARANTINO, MAYRA) (Entered: 06/19/2014)
06/19/2014	177	MARKMAN OPENING BRIEF OF PLAINTIFFS (LIZZA, CHARLES) (Entered: 06/19/2014)
		* * * * *
07/17/2014	181	MARKMAN RESPONSE BRIEF re 177 Markman Opening Brief, 176 Markman Opening Brief (Attachments: # 1 Declaration of Angela C. Ni, # 2 Certificate of Service) (LIZZA, CHARLES) (Entered: 07/17/2014)
07/17/2014	182	MARKMAN RESPONSE BRIEF re 177 Markman Opening Brief (Attachments: # 1 Declaration of Brendan F. Barker, # 2 Exhibit 1 to Declaration of Brendan F. Barker, # 3 Exhibit 2 to Declaration of Brendan F. Barker, # 4 Exhibit 3 to Declaration of Brendan F. Barker, # 5 Exhibit 4 to Declaration of Brendan F. Barker, # 6 Exhibit 5 to Declaration of Brendan F. Barker, # 7 Exhibit 6 to Declaration of Brendan F. Barker, # 8 Exhibit 7 to Declaration of Brendan F. Barker, # 9 Exhibit 8 to Declaration of Brendan F. Barker, # 10 Exhibit 9 to Declaration of Brendan

DATE	NO.	PROCEEDINGS
		F. Barker, # 11 Exhibit 10 to Declaration of Brendan F. Barker, # 12 Exhibit 11 to Declaration of Brendan F. Barker, # 13 Exhibit 12 to Declaration of Brendan F. Barker, # 14 Exhibit 13 to Declaration of Brendan F. Barker, # 15 Exhibit 14 to Declaration of Brendan F. Barker, # 16 Exhibit 15 to Declaration of Brendan F. Barker, # 17 Exhibit 16 to Declaration of Brendan F. Barker) (PATUNAS, MICHAEL) (Entered: 07/17/2014)
		* * * * *
09/05/2014	188	MOTION for Partial Summary Judgment *of Non Infringement of US Patent No. 8,598,219* by SANDOZ INC. (Attachments: # 1 Text of Proposed Order) (ABRAHAM, ERIC) (Entered: 09/05/2014)
09/05/2014	189	BRIEF *in Support of Motion for Partial SJ of Non Infringement of U.S. Patent No. 8,598,219* (ABRAHAM, ERIC) (Entered: 09/05/2014)
		* * * * *
09/05/2014	193	MOTION for Partial Summary Judgment *of Non-Infringement of U.S. Patent No. 8,598,219* by DR. REDDY'S LABORATORIES,

DATE	NO.	PROCEEDINGS
		INC., DR. REDDY'S LABORATORIES, LTD. (Attachments: # 1 Memorandum of Law, # 2 Imbacuan Declaration, # 3 Exhibits to Imbacuan Declaration, # 4 Rule 56.1 Statement, # 5 Text of Proposed Order, # 6 Certificate of Service) (IMBACUAN, MICHAEL) (Entered: 09/05/2014)
09/05/2014	194	MOTION for Summary Judgment *of Invalidity of US Patent 8,598,219* by SANDOZ INC. (Attachments: # 1 Text of Proposed Order) (ABRAHAM, ERIC) (Entered: 09/05/2014)
		* * * * *
09/05/2014	201	MOTION for Partial Summary Judgment *of Non-Infringement* by TEVA PHARMACEUTICAL INDUSTRIES, LTD., TEVA PHARMACEUTICALS USA, INC. (Attachments: # 1 Declaration Brendan F. Barker, # 2 Exhibit 1, # 3 Exhibit 5, # 4 Text of Proposed Order) (TARANTINO, MAYRA) (Entered: 09/05/2014)
09/05/2014	202	MEMORANDUM in Support filed by TEVA PHARMACEUTICAL INDUSTRIES,LTD., TEVA PHARMACEUTICALS USA, INC. re 201 MOTION for Partial

DATE	NO.	PROCEEDINGS
		Summary Judgment *of Non-Infringement* (Attachments: # 1 Statement Pursuant to Rule 56.1, # 2 Exhibit 2, # 3 Exhibit 3, # 4 Exhibit 4, # 5 Exhibit 6, # 6 Exhibit 7, # 7 Exhibit 8, # 8 Exhibit 9, # 9 Exhibit 10, # 10 Exhibit 11, # 11 Exhibit 12, # 12 Exhibit 13, # 13 Exhibit 14, # 14 Exhibit 15, # 15 Exhibit 16, # 16 Exhibit 17, # 17 Exhibit 18) (TARANTINO, MAYRA) (Entered: 09/05/2014)
		* * * * *
09/05/2014	204	BRIEF in Support filed by SANDOZ INC. re 194 MOTION for Summary Judgment *of Invalidity of US Patent 8,598,219* (ABRAHAM, ERIC) (Entered: 09/05/2014)
		* * * * *
09/05/2014	206	MOTION for Summary Judgment *of Infringement of U.S. Patent No. 8,598,219* by HELSINN HEALTHCARE S.A., ROCHE PALO ALTO LLC. (Attachments: # 1 Text of Proposed Order, # 2 Certificate of Service) (LIZZA, CHARLES) (Entered: 09/05/2014)
09/05/2014	207	BRIEF *In Support of Plaintiffs' Motion for Summary Judgment of Infringement of U.S. Patent No.*

DATE	NO.	PROCEEDINGS
		8,598,219 (Attachments: # 1 Statement of Material Facts Not In Dispute, # 2 Declaration of D. Weir Part 1, # 3 Declaration of D. Weir Part 2, # 4 Declaration of D. Weir Part 3, # 5 Declaration of D. Weir Part 4, # 6 Declaration of D. Weir Part 5, # 7 Declaration of D. Weir Part 6) (LIZZA, CHARLES) (Entered: 09/05/2014)
09/05/2014	208	MOTION for Partial Summary Judgment *of No Invalidity* by HELSINN HEALTHCARE S.A., ROCHE PALO ALTO LLC. (Attachments: # 1 Text of Proposed Order, # 2 Certificate of Service) (LIZZA, CHARLES) (Entered: 09/05/2014)
09/06/2014	209	BRIEF (Attachments: # 1 Statement of Material Facts Not in Dispute, # 2 Declaration, #3 Declaration, # 4 Declaration, # 5 Declaration, # 6 Declaration, # 7 Declaration, # 8 Declaration, # 9 Declaration, # 10 Declaration, # 11 Declaration, # 12 Declaration, # 13 Declaration, # 14 Declaration, # 15 Declaration, # 16 Declaration, # 17 Declaration) (LIZZA, CHARLES) (Entered: 09/06/2014)
* * * * *		

DATE	NO.	PROCEEDINGS
10/02/2014	219	BRIEF *in Support of Plaintiffs' Motion for Partial Summary Judgment of No Invalidity (Public Version)* (Attachments: # 1 Statement of Material Facts Not in Dispute (Public Version), # 2 Declaration of D. Weir - Part 1 (Public Version), # 3 Declaration of D. Weir - Part 2 (Public Version), # 4 Declaration of D. Weir - Part 3 (Public Version), # 5 Declaration of D. Weir - Part 4 (Public Version), # 6 Declaration of D. Weir - Part 5 (Public Version), # 7 Declaration of D. Weir - Part 6 (Public Version)) (LIZZA, CHARLES) (Entered: 10/02/2014)
		* * * * *
10/06/2014	221	RESPONSE in Opposition filed by DR. REDDY'S LABORATORIES, INC., DR. REDDY'S LABORATORIES, LTD. re 206 MOTION for Summary Judgment *of Infringement of U.S. Patent No. 8,598,219* (Attachments: # 1 Declaration of Michael Imbacuan, # 2 Statement in Response to R. 56.1 Statement, # 3 Certificate of Service) (SENDER, STUART) (Entered: 10/06/2014)
		* * * * *

DATE	NO.	PROCEEDINGS
10/06/2014	225	BRIEF in Opposition filed by HELSINN HEALTHCARE S.A., ROCHE PALO ALTO LLC re 193 MOTION for Partial Summary Judgment *of Non-Infringement of U.S. Patent No. 8,598,219*, 188 MOTION for Partial Summary Judgment *of Non Infringement of US Patent No. 8, 598,219*, 201 MOTION for Partial Summary Judgment *of Non-Infringement* (Attachments: # 1 Response to Teva's Rule 56.1 Statement, # 2 Response to DRL's Rule 56.1 Statement, # 3 Response to Sandoz's Rule 56.1 Statement, # 4 Declaration of D. Weir, # 5 Exhibit to D. Weir Declaration, # 6 Certificate of Service) (LIZZA, CHARLES) (Entered: 10/06/2014)
10/06/2014	226	BRIEF in Opposition filed by DR. REDDY'S LABORATORIES, INC., DR. REDDY'S LABORATORIES, LTD., SANDOZ INC., TEVA PHARMACEUTICAL INDUSTRIES, LTD., TEVA PHARMACEUTICALS USA, INC. re 208 MOTION for Partial Summary Judgment *of No Invalidity* (Attachments: # 1 Certificate of Service) (ABRAHAM, ERIC) (Entered: 10/06/2014)

DATE	NO.	PROCEEDINGS
10/06/2014	227	BRIEF in Opposition filed by HELSINN HEALTHCARE S.A., ROCHE PALO ALTO LLC re 194 MOTION for Summary Judgment *of Invalidity of US Patent 8,598,219* (Attachments: # 1 Response to Sandoz's Rule 56.1 Statement of Undisputed Facts, # 2 Declaration of J. Buckingham, # 3 Declaration of C. Peck - Part 1, # 4 Declaration of C. Peck - Part 2, # 5 Declaration of C. Peck - Part 3, # 6 Declaration of C. Peck - Part 4, # 7 Declaration of C. Peck - Part 5, # 8 Declaration of C. Peck - Part 6, # 9 Certificate of Service) LIZZA, CHARLES) (Entered: 10/06/2014)
		* * * * *
10/27/2014	230	REPLY to Response to Motion filed by DR. REDDY'S LABORATORIES, INC., DR. REDDY'S LABORATORIES, LTD. re 193 MOTION for Partial Summary Judgment *of Non-Infringement of U.S. Patent No. 8,598,219* (Attachments: # 1 Certificate of Service) (SENDER, STUART) (Entered: 10/27/2014)
10/27/2014	231	REPLY BRIEF to Opposition to Motion filed by SANDOZ INC. re 194 MOTION for Summary Judgment *of Invalidity of US Patent*

DATE	NO.	PROCEEDINGS
		8,598,219 (Attachments: # 1 Certificate of Service) (ABRAHAM, ERIC) (Entered: 10/27/2014)
10/27/2014	232	REPLY BRIEF to Opposition to Motion filed by SANDOZ INC. re 188 MOTION for Partial Summary Judgment *of Non Infringement of US Patent No. 8, 598,219* (Attachments: # 1 Certificate of Service) ABRAHAM, ERIC) (Entered: 10/27/2014)
		* * * * *
10/27/2014	234	REPLY BRIEF to Opposition to Motion filed by TEVA PHARMACEUTICAL INDUSTRIES, LTD., TEVA PHARMACEUTICALS USA, INC. re 201 MOTION for Partial Summary Judgment *of Non-Infringement* (Attachments: # 1 Declaration Cory Wohlbach, # 2 Exhibit Wohlbach Ex. A, # 3 Exhibit Wohlbach Ex. B, # 4 Exhibit Wohlbach Ex. C, # 5 Exhibit Wohlbach Ex. D, # 6 Exhibit Wohlbach Ex. E, # 7 Exhibit Wohlbach Ex. F, # 8 Exhibit Wohlbach Ex. H, # 9 Exhibit Barker Ex. 2, # 10 Exhibit Barker Ex. 4) (TARANTINO, MAYRA) (Entered: 10/27/2014)
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DATE	NO.	PROCEEDINGS
10/27/2014	236	REPLY BRIEF to Opposition to Motion filed by HELSINN HEALTHCARE S.A., ROCHE PALO ALTO LLC re 208 MOTION for Partial Summary Judgment *of No Invalidity* (Attachments: # 1 Statement Response to Sandoz Inc.s Additional Statement of Material Facts in Support of Defendants Opposition to Plaintiffs Motion for Partial Summary Judgment of No Invalidity, # 2 Declaration of Steven Pollack, # 3 Exhibit 98-104 of Pollack Decl., # 4 Exhibit 105-106 of Pollack Decl., # 5 Exhibit 107-109 of Pollack Decl., # 6 Certificate of Service) (LIZZA, CHARLES) (Entered: 10/27/2014)
10/27/2014	237	REPLY BRIEF to Opposition to Motion filed by HELSINN HEALTHCARE S.A., ROCHE PALO ALTO LLC re 206 MOTION for Summary Judgment *of Infringement of U.S. Patent No. 8,598,219* (Attachments: # 1 Declaration of Dana Weir, # 2 Certificate of Service) (LIZZA, CHARLES) (Entered: 10/27/2014)
* * * * *		
04/22/2015	290	MEMORANDUM OPINION filed. Signed by Judge Mary L. Cooper

DATE	NO.	PROCEEDINGS
		on 4/22/2015. (kas,) (Entered: 04/22/2015)
		* * * * *
05/19/2015	307	ORDER denying without prejudice 193 Motion for Partial Summary Judgment; denying without prejudice 201 Motion for Partial Summary Judgment; denying without prejudice 206 Motion for Summary Judgment ; denying without prejudice 208 Motion for Partial Summary Judgment. Signed by Judge Mary L. Cooper on 5/19/2015. (mmh) (Entered: 05/19/2015)
		* * * * *
05/21/2015	311	TRIAL BRIEF by HELSINN HEALTHCARE S.A., ROCHE PALO ALTO LLC. (Attachments: # 1 Certificate of Service) (LIZZA, CHARLES) (Entered: 05/21/2015)
05/21/2015	312	TRIAL BRIEF by TEVA PHARMACEUTICAL INDUSTRIES, LTD., TEVA PHARMACEUTICALS USA, INC. (TARANTINO, MAYRA) (Entered: 05/21/2015)
		* * * * *
11/13/2015	360	MEMORANDUM OPINION. Signed by Judge Mary L. Cooper on 11/13/15. (eh,) (Entered: 11/16/2015)

DATE	NO.	PROCEEDINGS
11/16/2015	361	Letter from Helsinn to the Hon. Mary L. Cooper, U.S.D.J. (LIZZA, CHARLES) (Entered: 11/20/2015)
		* * * * *
03/03/2016	381	SUPPLEMENTAL OPINION. Signed by Judge Mary L. Cooper on 3/3/16. (eh,) (Entered: 03/03/2016)
		* * * * *
02/06/2018	401	ORDER & JUDGMENT VACATING THE FINAL JUDGMENT (DE No. 361) entered on November 16, 2015, including any and all relief under 35 U.S.C. § 271(e)(4)(A) and (B), thus permitting FDA to grant final approval to ANDA No. 090713. The order that the effective date of any final approval of ANDA No. 090713 shall be no earlier than July 30, 2024, is VACATED, etc. Signed by Judge Stanley R. Chesler on 2/6/18. (cm,) (Entered: 02/06/2018)

SUMMARY

Title of Study: A Dose-Ranging Efficacy, Safely, and Pharmacokinetic Study of Single Intravenous Doses of RS-26269 for Prevention of Nausea and Vomiting in Chemotherapy-Naive Cancer Patients Receiving Highly Emelogenic Chemotherapy

Study No. and RS No.: 2525952330 and RS-25259-197

Investigators and Study Centers: Multiple

Publications: None

Study Period: April 1994—April 1995

Clinical Phase: II

Objectives: The objectives of This study ware to (1) determine the dose-response relationship among single IV doses of RS-25259 over the dose range 1-90 ug/kg: the primary endpoint was the proportion of patients with a complete antiemetic response (no vomiting or retching) for 24 hours after highly emelogenic chemotherapy in chemotherapy-naive cancer patients; the efficacy of each dose was compared with the efficacy of the lowest dose; (2) assess the safety of single IV doses of RS-25259 administered over the range of doses tested in this patient population; and (3) assess the pharmacokinetics of single IV doses of RS-25259 over the range of doses lasted in This patient population.

Methodology: This was a randomized, double-blind, multicenter, dose-ranging efficacy, safety, and pharmacokinetic study of IV RS-25259-197. Patients were randomized to receive one of five doses of study drug and ware observed as Inpatients and/or outpatients. Safety and efficacy evaluations were recorded periodically during the first 24 hours and then daily for the

next 6 days following administration of study medication. Additionally, each patient was contacted 14 days postdosing to obtain further salary information. Blood samples for pharmacokinetic analysis were taken from patients at selected investigational sites before dosing and at various limes up to 168 hours after dosing with study drug; the plasma portion was assayed tor RS-25259 and RS-17825 (the N-oxide metabolite) concentrations, from which pharmacokinetics parameters were computed.

Number of Subjects: One hundred sixty-one patients (129 males. 32 females), 23-79 years of age were enrolled in this study. All patients are included in the safety evaluations. However, 13 patients were excluded from ail efficacy analysis. Reasons for exclusion included various protocol violations (8 patients). Subsequently to establishing evaluability, 5 additional patients, all of whom received cyclophosphamide, were also excluded. Thus, efficacy analyses focused on only patients who received cisplatin-based chemotherapy. The distribution of evaluable patients by dose group is as follows: 0.3-1 ug/kg, 29 patients; 3 ug/kg. 24 patients; 10 ug/kg. 25 patients; 30 ug/kg, 24 patients; and 90 ug/kg, 45 patients.

Diagnosis and Criteria for Inclusion: Patients were men and women who had histologically proven cancer, were chemotherapy naive, and were scheduled to receive their first dose of emelogenic chemotherapy, either cisplatin (> 70 mg/m2) or cyclophosphamide (> 1100 mg/m2).

Test Product Dose and Mode of Administration, Formulation No., Batch/Lot No.: RS-25259 was supplied in 5-mL glass vials at a concentration of 500 ug/mL, Patients were randomly assigned to one of five RS-25259 treatments. Prior to Amendments lit and IV of

the protocol, the treatments were 0.3,1, 3, 10, or 30 ug/kg; following those amendments, they were 1, 3, 10, 3e, or 90 ug/kg Normal saline was used to dilute RS-25259 to a total injection volume of 25 mL. Study drug was administered 30 minutes before start of chemotherapy and given as a single bolus IV dose over 30 seconds. The formulation number RS-25259 was No. F25259-006 (Lot Nos. 25259-197-12479 and 1021881),

Reference Therapy, Dose and Mode of Administration, Formulation No., Batch/Lot No.: None

Duration of Treatment: Patients received a single IV dose of RS-25269-197 over 30 seconds and wars subsequently followed for a total of 14 days.

Criteria for Evaluation: Clinical Data—The primary efficacy variable was the proportion of patients with a complete antiemetic response (no vomiting or retching, no rescue medication) for 24 hours after the start of chemotherapy. The efficacy of each dose was compared with the efficacy of the lowest dose. Secondary efficacy variables included the time to the first emetic episode, lime to administration of rescue therapy, area under the nausea-intensity-by-time (NIT) curve based on categorical scale, time to treatment failure (either emesis or need for rescue medication, whichever occurred first), proportion of patients with complete control of emesis (no vomiting and only mild nausea or no nausea), and global rating of satisfaction with the control of nausea and vomiting based on a visual analog scale. These variables were supplemented by physical examination and vital signs data, laboratory findings, and adverse event data. Pharmacokinetic Data—Plasma concentrations and computed Pharmacokinetic parameters for RS-25259 and RS-17825 were assessed.

Statistical Methods: Demographic and safety data were summarized; plasma concentrations and computed pharmacokinetic parameters were listed and statistically summarized by dose group; individual and mean plasma concentrations were plotted versus time; and computed parameters were analyzed for a dose relationship (e.g., close proportionality, dose linearly).

Summary and Conclusions: RS-25259, administered as a single bolus intravenous injection of 3, 10. 30 or 90 ug/kg 30 minutes prior to high-dose cisplatin chemotherapy, was effective in suppressing chemotherapy-induced emesis for 24 hours. All Four doses were approximately equally effective as compared with the combined results from a cohort of 0.3 and 1 ug/kg. The following table summarizes key efficacy parameters.

Parameters	RS-25259 Dose (ug/kg)				
	0.3-1	3	10	30	90
% Complete Control (24 hours)	24	46	40	50*	46
Complete Response (24 hours)	24	39	40	48	46
Median Time (hours) to Failure (first emetic episode or rescue Rx	5.6	22.7*	19.0	> 24*	21.8*

*statistically significant differences ($p < 0.05$) vs. lowest dose group

Safety evaluations and comparisons made between treatment groups all suggest that RS-25259 is a relatively safe therapeutic agent. No dose response-related adverse events were observed. One hundred twenty-nine of the 16 patients in the safety analyses (80.1%) experienced at least one adverse event during the study. A majority of events were rated as mild or moderate (469/559, 83.9%) and were considered probably not related to test medication (481/559. 86.0%). incidence, frequency, severity, and relationships of adverse events appeared to be essentially equally distributed among the RS-25259 treatment groups. The most frequent adverse event reported was headache, followed by constipation, pain, asthenia, anorexia, and diarrhea. Serious adverse events that occurred were all judged by the treating physicians to be probably not related to chemotherapy. No dose-related toxicity was observed in electrocardiograms or laboratory parameters evaluations.

Plasma AUC of RS-25259 Increased with increases in dose, and kinetics of RS-25259 were shown to be dose Proportional over the range of doses in this study (1-90 ug/kg) The mean observed T___ ranged from 8.6 to 49.6 minutes postdosing, although appreciable plasma concentrations of RS-25259, well above the limit of quantitation, were measured in the first sample drawn for nearly all patients at all dose levels. Mean C___ ranged from 0.880 to 336 ng/mL over the five dose levels. The mean half-life of RS-25259 ranged from 43.7 to 128 hours. Three patients had very long half-lives of 210, 246, and 383 hours. Mean values of clearance and volume al distribution ranged from 1.51 to 2.23 mL/min/kg and 6.83 to 12.5 L/kg respectively, over the five dose levels. There were no statistically significant differences in plasma concentrations or computed parameters over the range of doses studied.

Many pharmacokinetic parameters for RS-17825 could not be determined for the 1, 3, and 10 ug/kg dose levels because of very low plasma concentrations. For this reason, dose proportionality could not be determined for RS-17825. The mean T___ of RS-17825 ranged from 0.208 to 112 hours and the mean

ranged from 0.0549 to 0.855 ng/mL across the live dose levels. The mean half-ere of RS-17826 averaged 59.1 and 110 hours at the two top dose levels for which it could be calculated (30 and 90 ug/kg). Several patients had long RS-17826 half-lives ranging from 106 to 434 hours. Across all five dose levels, C___ and T___ showed statistically significant differences, but $AUC_{0\text{-}24}$, did not. Hall-life and total AUC were not statistically different across the two top dose levels for which they could be calculated_ The mean AUC ratio of RS-17825 to RS-25259 total AUG averaged 4.1178 and 0.0789 and indicated a small presence in plasma of the N-cxide metabolite relative to the RS-25259 parent compound.

Based on the results of this study, a dose of 3 ug/kg or 10 ug/kg RS-25259 might be appropriate for further development. Pharmacokinetically, RS-25259 demonstrated dose-proportional kinetics with no statistically significant differences in parameters across the five dose levels. The plasma half-life was exceptionally long for this class of compound, arid a few patients demonstrated very long half-lives compared with the other patients. Human exposure to the N-oxide metabolite (RS-17825) in the plasma was minor relative to the parent compound.

/s/ Wolfgang B. Strauss, B.Sc. Sept 25, 95

Wolfgang B. Strauss, B.Sc. Date

Center for Clinical Research Physicians

/s/ Daniel L. Combs, B.S. — Sept 25, 95
Daniel L. Combs, B.S. — Date
Center for Clinical Pharmacology
and Clinical Pharmacokinetics

/s/ Gil Fine — Sept 25, 95
Gil Fine, Ph.D. — Date
Center for Biometrics and
Database Management

Confidential

Meeting Minutes

re	Helsinn Palonosetron Team Meetings
Location	3S5 Sherman Ave., Suite 5, Palo Alto, CA 94306
Date and time	Monday July 20, 1998 – Friday July 24, 1998
Attendees	Monday July 20 attendees Mr. Dario Ceriani, Alberto Macciocchi, M.D., Bob Hill Ph.D., and Martha A. Reitman M.D.

Tuesday July 21 attendees Mr. Dario Ceriani. Alberto Macciocchi, MD., Martha A. Reitman M.D., [Alan Krubiner Ph.D., attorney (lunch meeting)]

Wednesday July 22 attendees Mr. Dario Ceriani, Alberto Macciocchi, MD., Martha A. Reitman M.D, Dr. Giorgio Calderari, Dr. Ron Pearl, Mr. Bob Ignaffo

Thursday July 23, Friday July 24 attendees Mr. Dario Ceriani, Alberto Macciocchi, M.D., Martha A. Reitman M.D. Dr. Giorgio Calderari, Tom Malcfyt, PhD., Chandu Hegde, Maryann Lee, Li-Hwa Lin, Don Curley, Hans Schmid (part-time)

Thursday July 23, Alberto Macciocchi, M.D., Dr. David Gandarra (University of California, Davis)

Thursday July 23 Roche-Syntex Lunch attendees Mr. Dario Ceriani, Martha A. Reitman M.D, Dr. Giorgio Calderari, Dr. Sharyn Solish, Mr. Wolff Strauss, Ms. Anne Hopkins, Mr. Bruce Kowalczek, Dr. Tom Malefyt, Dr. Pity Penumarthy. Ms. Barbara Simkin

Friday, July 24 attendees Mr. Dario Ceriani, Alberto Macciocchi, M.D., Martha A. Reitman M.D, Dr. Giorgio Caiderari, Ms. Gayle Mills, Ms. Anne Hopkins

CINE study designs There are two ways to set up the high dose trial. Comparison of all groups with the low dose of Palo, or comparison between each dose and ondansetron.

The low dose should not be too low (not ethical). The proposal is to test effective doses seen in Phase 2 (3. 10, and 30 ug/kg) compared to ondansetron 32 mg.

0.25, 0.75 and 2 mg are she three proposed doses (to be confirmed by the phase 2 analyses outlined above). The volume is planned to be 5 ml.

The definitions of CR (no emesis, no rescue medication) and CC (no nausea, no emesis, no rescue medication) were confirmed. CC at 24 hours will be the primary efficacy endpoint. Continued control beyond 24 hours will be a secondary endpoint. Missing data will be counted as a treatment failure.

The management of dexamethasone in the trial and the evaluation of repeat cycles will need further discussion.

PONV 1. Ina review of 2500, the median time to first emesis was evaluated (it is long for placebo and the treatment groups). It was determined that this was without regard to the use of rescue medication, and a review of complete responders (table 16A and figure 5) was more in keeping with Dr. Pearl's experience.

2. The dose which provides efficacy is L ug/kg, with the possibility that 3 ug/kg is more effective. The trial will include both doses. Doses planned include 0.1 mg and 0.3 mg (in 2 m1).

3. An analysis by sex and ug/kg converted to mg is planned to confirm these doses.

4. A review of dolasetron and ondansetron demonstrated that that multiple doses were assessed in phase 3. For dolasetron PONV prophylaxis, three trials were conducted (N on treatment = approximately L600) and for PONV treatment, two trials were conducted (N on treatment= approximately 800). It needs to be determined whether a program for prophylaxis only would be acceptable to FDA.

Continued on next page

A Double-Blind Clinical Study to Compare Single IV Doses of Palonosetron, 0.25 mg or 0.75 mg, and Ondansetron, 32 mg IV, in the Prevention of Moderately Emetogenic Chemotherapy-Induced Nausea and Vomiting

Protocol No. PALO-99-03

Sponsor:
Helsinn Healthcare SA
P.O. Box 357
5915 Pambio-Noranco (Lugano)
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Telephone: (091) 985 21 21
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Protocol Date: 15 November 1999

Confidential Information

The information contained in this document is confidential. Acceptance of this document constitutes agreement by the recipient that no information contained herein will be published or disclosed without prior written authorization front an official of Helsinn Healthcare SA, except that this document may be disclosed to appropriate Institutional Review I Boards

and Ethics Committees or duly authorized representatives of a national regulatory authority under the condition that they are requested to keep it confidential:

1.0 INTRODUCTION

1.1. Background and Rationale

Nausea and vomiting are among the most unpleasant and distressing subjective side effects of cancer chemotherapy (1,2). Chemotherapy-induced nausea and vomiting (CINV) reduces a patient's quality of life (3) and may cause non-compliance or refusal of potential life-saving chemotherapeutic regimens (2). Although the severity and pattern of nausea and vomiting induced by a chemotherapeutic regimen depend on the agents used and the doses employed (4), The neuropharmacology of highly or moderately emetogenic CINV is similar (5).

Research into preventing CINV has been directed at blocking receptors for neurotransmitters, such as dopamine, 5-hydroxytryptamine (5-HT, scrotonin), endorphin, and substance P, which are found in the brainstem vomiting center. The initial clinical research was focused on blocking dopamine receptors with metoclopramide, phenothiazines and butyrophenones (6). Metoclopramide was later found to bind with the 5-HT receptor (6). Data indicating that nausea and vomiting may be triggered by the release of 5-HT involving both the gastrointestinal tract and the central nervous system lead to the important discovery of the selective 5-HT, receptor antagonists; ondansetron. granisetron, and dolasetron (7). These agents have demonstrated greater selective antiemetic effects than high doses of metoclopramide (8-10). In addition, 5-HT, receptor antagonists have been well tolerated and free of extrapyramidal toxicity

which is occasionally reported with agents which block dopamine transmission. When administered alone (9-12) or in combination with dexamethasone (13-15), 5-HT, receptor antagonists offer better anti-emetic control of CINV than other presently marketed classes of anti-emetics.

Palonosetron is a novel, potent, and selective 5-HT receptor antagonist. It has been evaluated as an anti-emetic for use in CINV and postoperative nausea and vomiting (PONV). In animal models of chemotherapy-induced emesis, palonosetron completely inhibits emesis in up to 100% of animals given high-dose cisplatin (16). In healthy, adult volunteers, the mean half-life of palonosetron, administered either IV or orally, is approximately 4.0 hours, which is 4 to 10 times longer than the currently marketed 5-HT, receptor antagonists [4 hours for ondansetron (17), 9 hours fur granisetron (18), and approximately 7 hours for the active metabolite of dolasetron (19)]. Results achieved in Phase H CINV studies suggest that palonosetron is safe and effective in preventing nausea and vomiting following emetogenic chemotherapy, especially during the first 24 hours after administration (16).

Given the high affinity of palonosetron for the 5-HT, receptor and efficacy results in both animal models and in Phase II studies, a single dose of palonosetron is expected to control acute CINV following moderately and highly emetogenic chemotherapy. Furthermore, due to the long half-life of palonosetron in humans, a single dose of palonosetron may also be beneficial in controlling the delayed phase (24-120 hours) of nausea and vomiting induced by a chemotherapeutic regimen. This study is designed to support the hypotheses that palonosetron is nor inferior to

currently available 5-HT, receptor antagonists and is effective in preventing nausea and vomiting following moderately emetogenic chemotherapy, regardless of the chemotherapy regimen. In this study, the active comparator chosen is odansetron, which is a selective 5-HT, receptor antagonist widely used in the prevention of MTV (10-14, 17, also see Appendix H).

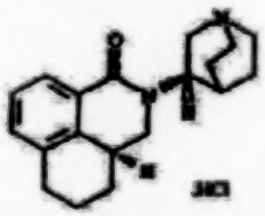
Based on the Phase II data (see Section 1.43), fixed doses of palonosetron. 025 mg (3 ug/kg) and 0.75 mg (10 ug/kg) were chosen as the optimal doses for the Phase ID trials.

1.2. Chemical and Pharmaceutical Properties of Palonosetron

1.2.1. Chemical Name an International Non-Proprietary Name (INN)

- (3aS-2-[(S)-I-Azabicyclo[2.2.2]oct-3-yl)-2,3,3a,4,5,6-hexahydro-1-oxo-1H-benx[de]isoquinoline hydrochloride
- Palonosetron hydrochloride

1.2.2. Chemical Structure



Palonosetron hydrochloride

Palonosetron is structurally unrelated to currently available 5-HT, receptor antagonists.

1.2.3. Pharmaceutical Formulations and Storage and Handling of Study Drug

The formulations to be used for the Phase DI clinical studies are sterile, isotonic, buffered solutions for IV administration alone or as an admixture with isotonic saline. The injectable solutions should be stored at room temperature and protected from exposure to direct light. Solutions that have inadvertently become frozen should not be used, but should be returned to the sponsor for disposal and replacement.

1.3. Preclinical Studies

Extensive *in vitro* and *in vivo* pharmacologic studies for palonosetron have been conducted. The key information from these studies are:

- Palonosetron has high affinity and specificity for 5-HT, receptors.

and/or solicited adverse event. Each subject received a single dose of palonosetron HCl or placebo. Individual doses were based on body weight. The doses ranged from 0.3-90 ug/kg for the IV studies, and from 3-80 ug/kg for the oral studies.

Phase I studies have characterized the safety and pharmacokinetics of palonosetron given IV and orally. The data indicate the following:

- Palonosetron was well tolerated up to doses of 90 ug/kg.
- There were no significant ECG abnormalities except one subject with brief asymptomatic episodes of second-degree A-V block and one episode of sinus exit block.
- Most frequent adverse events were headache, constipation, abdominal pain, and transiently elevated liver enzymes which did not appear dose-related. Adverse events were generally mild to moderate.

1.4.2. Human Pharrnacokinetics

The mean maximum plasma concentration (C___) and area under the concentration-time curve (AUC) were generally proportional to dose after IV and after oral dosing in healthy subjects, as well as postoperative and cancer patients. The mean time to maximum plasma concentration (T___) after oral administration was generally 4-6 hours. The mean plasma elimination half-life (T___) was approximately 40 hours in subjects given single IV or oral doses. Approximately 50% of palonosetron is metabolized and about 40% is renally cleared unchanged. The major metabolite found in plasma is the N-oxide metabolite (Metabolite 9). in virro studies using human plasma have shown that palonosetron hydrochloride is 62% plasma-protein bound over the range of concentrations (5-412 ng/mL).

1.4.3. Phase II Studies

Several Phase II studies have been conducted to evaluate safety and efficacy of palonosetron HCl including one clinical trial (study 2330) of intravenous palonosetron Ha and one oral study (study 2332) in the prevention of highly emetogenic CINV. There were two additional clinical trials conducted for post-operative nausea and vomiting run concurrently with the CINV program: one utilized intravenous and one utilized oral administration (2500 and 2502, respectively). Data from studies 2332, 2500 and 2502 contribute to an understanding of the overall safety profile of palonosetron HCl.

Study 2330 was a randomized, double-blind, multicenter, dose-ranging design. It evaluated the efficacy, safety, and pharmacokinetics of single intravenous doses of palonosetron HCl for the prevention of nausea

and vomiting in patients receiving highly emetogenic chemotherapy. All patients were chemotherapy naive, had histologically-proven cancer and received either cisplatin (>70 mg/m2) or cyclophosphamide (>1100 mg/m2). Thirty minutes before administration of the chemotherapeutic agent(s), study drug was administered by IV bolus over 30 seconds. The original protocol called for patients to receive one of five IV doses of palonosetron (0.3, I, 3, 10, or 30 ug/kg). Based on the early blinded data from a limited number of patients the protocol was amended to discontinue the lowest dose (0.3 ug/kg) and to add a higher dose (90 ug/kg) for a new treatment. The 03 ug/kg patients were merged with the 1 ug/kg patients to form a 0.3-1 ug/kg group.

One hundred sixty one patients (129 males, 32 females), 23-79 years of age were enrolled in this study to obtain 148 evaluable patients. All evaluable patients received cisplatin-based chemotherapy. The distribution of evaluable patients by dose group was as follows: 0.3-1 ug/kg palonosetron, 29 patients; 3 ug/kg, 24 patients; 10 ug/kg, 25 patients; 30 ug/kg, 24 patients: and 90 ug/kg, 46 patients. Patients were evaluated periodically during the first 24 hours following administration of chemotherapy then daily for 7 days and again at 14 days post chemotherapy fora final safety review.

The primary efficacy variable was the proportion of patients with a complete anti-emetic response (CR, no vomiting or retching and no rescue medication) for 24 hours after the start of chemotherapy. The efficacy of each dose was compared with the efficacy of the lowest dose. Secondary efficacy variables included the time to the first emetic episode, time to rescue therapy, area under the nausea intensity-by-time (NTT) curve based on categorical scale, time to treatment failure (either

emesis or administration of rescue medication, whichever occurred first), proportion of patients with complete control of emesis (CC, no emetic episodes, only mild nausea or no nausea and no rescue medication for 24 hours after the start of chemotherapy), and global rating of satisfaction with the control of nausea and vomiting. These variables were supplemented by physical examination and vital signs data, laboratory findings, ECGs, and adverse event data.

The following table summarizes the results for the following parameters:

a) Complete response (CR)

b) Complete control (CC)

c) Median time to failure

Study 2330

Summary of Patients' Responses for 24 Hours After Chemotherapy (Evaluable Patients)

	0.3-1 ug/kg	3 ug/kg	10 ug/kg	30 ug/kg	90 ug/kg
n	29	24	25	24	46
% with CR	24%	46%	40%	50%	46%
p-Value[a]	–	0.103	0.079	0.047	0.128
n	29	23	25	23	46
% with CC	24%	39%	40%	48%	46%
p-Value[a]	–	0.178	0.079	0.079	0.128
n	29	24	25	24	46
Time to Failure (hr) (median)	5.6	22.7	19.0	> 24	21.8
p-Value[a]	–	0.011	0.098	0.010	0.004

*p-value for comparison with low-doses (0.3-1 ug/kg) treatment group

Data from this study clearly demonstrate that the 3 ug/kg dose of palonosetron is the minimal effective dose in preventing CINV. The results of this study also suggest that palonosetron is a well tolerated compound. Although 129 (80.1%) patients experienced at least one adverse event during the study (14 days of observation), the majority of events (83.9%) were rated as mild or moderate and relationship to test medication was usually considered "probably not related" (86.0%). Adverse events were essentially equally distributed across the various dose groups and no dose response effects are apparent. Evaluations of ECGs and laboratory parameters were uneventful, confirming palonosetron tolerance.

The most frequently reported adverse events, occurring in 5% or more of the total number of patients who received palonosetron in the Phase I and Phase II studies, were: headache, constipation, fever, abdominal pain, diarrhea, itching (pruritus), pain, asthenia, and insomnia. In addition, dizziness and anorexia were reported in more than 5% of the patients who received > 30 ug/kg of palonosetron, and back pain was reported in more than 5% of the patients who received 10-20 ug/kg of palonosetron. Instances of an increase in liver enzymes, tachycardia, bradycardia, abnormal electrocardiograms, chest pain (angina), hypotension, and hypertension have also been mooned.

For further information about palonosetron, please refer to the Investigator's Brochure 06).

2.0 OBJECTIVES OF THE STUDY

2.1. Primary

- To compare the efftcacy of single IV doses of palonosetron, 0.25 mg or 0.75 mg, to ondansetron 32 mg IV in preventing moderately emetogenic CINV.

2.2. Secondary

- To evaluate the safety and tolerability of palonosetron and its relative safety in comparison with ondansetron.
- To evaluate the effect of anti-emetic control with palonosetron or ondansetron on the quality of life of patients receiving moderately emetogenic chemotherapy.

3.0 STUDY DESIGN

This is a multicenter, Phase III, randomized, balanced, controlled, double-blind, double-dummy, parallel, stratified, and active comparator study design comparing the efficacy, safety and tolerability of single IV doses of palonosetron, 0.25 mg or 0.75 mg, with a single IV dose of ondansetron 32 mg, in the prevention of moderately emetogenic WV. The active comparator, ondansetron 32 mg, is the U.S. FDA-approved IV regimen for the prevention of nausea and vomiting following moderately emetogenic chemotherapy. This dose is also normally used in Europe for the prevention of CAN. Implementation of published historical placebo controls will be used to validate the trial, demonstrating its sensitivity. It is

Helsinn Announces That Patient Enrollment For Phase III Palonosetron Trials Progresses Both in the USA and Europe.

Date: Sep 14, 2000

Words: 367

Publication: PR Newswire

LUGANO, Switzerland, Sept. 14 /PRNewswire/ –

Helsinn Healthcare SA announced today that the enrollment of the patients for Phase III clinical trials is progressing as scheduled. The patients are treated with Palonosetron, a novel treatment for the prevention of chemotherapy induced nausea and vomiting. Palonosetron is expected to provide an extended antiemetic coverage to cancer patients versus the existing 5-HT3 receptor antagonists thus reducing the need of multiple administrations.

The company will enroll over 1,800 patients in multicenter, randomized, balanced, controlled, double-blind, stratified, parallel and active comparator design studies. The Phase III efficacy protocols have been approved by the FDA according to the Modernization Act procedures (FDAMA). The trials will be conducted in about 80 already active centers across North America (40 centers) and Europe (40 centers).

"The Phase 11 trials demonstrated the efficacy of Palonosetron in the prevention of emesis with no significant side effects on the cardiovascular, respiratory, gastrointestinal, CNS and renal systems," said Luigi Baroni M.D., Director of Scientific Affairs. "We are now eager to complete the data necessary for the NDA filing scheduled for early 2002."

Additionally, both the technology transfer of the Palonosetron synthesis process from the originator's

plant and the development of the i.v. finished dosage form have been succesfully accomplished.

"I am pleased to see the completion of the production of the first batch of Palonosetron active ingredient at Helsinn's new state-of-the-art facility (Helsinn Advanced Synthesis SA) dedicated to the production of high-potency active ingredients. Upon market approval, Helsinn will be in the position to supply its marketing partners with a finished product ready for distribution," said Giorgio Calderari, Director, Technical Affairs.

Helsinn is seeking marketing partners for this patented product in different territories.

Helsinn is a privately owned pharmaceutical group with headquarters in Switzerland. Helsinn's core business is licensing. The company's business strategy is to in-license new chemical entities at a certain stage of development. Helsinn completes the development by performing pre-clinical and clinical studies as well as chemical and pharmaceutical development through the attainment of market approval in strategic markets (USA and Europe). The finished products are manufactured at Helsinn and out-licensed to its marketing partners for distribution.

Additional information is available at www.helsinn.com.

License Agreement

between

HELSINN HEALTHCARE SA

and

MGI PHARMA, INC.

for

PALONOSETRON

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THIS AGREEMENT (hereinafter called "Agreement") is effective as of this 6th day of April 2001 (hereinafter called "Effective Date), between HELSINN HEALTHCARE SA, a corporation organized and existing under the law of Switzerland and having its registered office at Via Pian Scairolo, 6912 Pazzallo, Switzerland (hereinafter called "HHC") of the one part, and MGI PHARMA, INC., a corporation organized and existing under the law of the state of Minnesota, United States of America and having its registered office at 6300 West Old Shakopee Road, Suite 110, Bloomington, MN 55438-2318, USA (hereinafter called "MGI"), of the other part.

RECITALS

a. HHC carries on business as a licensing company, product developer and pharmaceutical trader and, in particular for the purpose of this Agreement, has inlicensed from the companies Syntex (U.S.A.) Inc. and F. Hoffmann-La Roche AG by means of a License Agreement dated June 23, 1998 (hereinafter, the "Syntex Agreement") world-wide exclusive rights to certain patents and know-how to make, have made, develop, register, market, distribute and sell, directly or indirectly, the Compound (as hereinafter defined) and pharmaceutical preparations containing said Compound as active pharmaceutical ingredient.

b. MGI carries on business as a pharmaceutical company and, in particular for the purpose of this Agreement, represents that it is a reputable pharmaceutical company, having a size and a position on the market adequate to effectively market, distribute and sell the Products (as hereinafter defined) and that it has the necessary sales force to successfully sell the Products in the Field throughout the Territory (as hereinafter defined).

c. Prior to entering into discussions with HHC, MGI possessed no technology and limited information of its own (including publicly available information) relating to the Compound and/or the Products. The Parties entered on 25th May 2000 into a Secrecy Agreement by means of which HHC disclosed to MGI confidential information and data relating to the Compound and Products.

d. The Parties entered on October 5th 2000 into a Letter of Intent on which basis they have performed respective appropriate due diligence for the purpose of establishing their interest and willingness to enter into this Agreement, and hereby confirm that (i) each has been provided with full and complete access to such information as they deemed necessary or appropriate to conduct due diligence, and (ii) such due diligence has been completed to their full satisfaction.

e. MGI now wishes to acquire the right to act as HHC's licensee and distributor for the Products in the Territory and HHC is willing to so appoint MGI under the terms and conditions hereinafter set forth.

f. The Parties agree that this preamble constitutes an integral part of this Agreement and all capitalized terms used in this preamble shall have the meaning as defined in Article I hereafter.

NOW, THEREFORE, in consideration of the foregoing and of the mutual covenants and conditions herein contained, the Parties hereby agree as follows:

ARTICLE 1 - DEFINITIONS

The following terms as used in this Agreement have, unless the context clearly indicates otherwise, the following meanings:

1.1 "Accounting Period" means the quarters ending 31st March, 30th June, 30th September and 31st December in each year throughout the term of this Agreement.

1.2 "Affiliate" means an organization that, whether now or in the future, controls, is controlled by or is under common control with a Party. For the purposes of this definition, the terms "controls," "controlled by," and "under common control with" as used with respect to any Party, means the. possession (directly or indirectly) of fifty percent or more of the voting stock or other equity interest of a subject entity with the power to vote, or the power in fact to control the management decisions of such entity through the ownership of securities or by contract or otherwise.

1.3 "Compound" means the active pharmaceutical ingredient (3aS-2-[(S)-1-Azabicyclo[2.2.2]oct.-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1H-benz[de]isoquinoline hydrochloride, having the generic name palonosetron hydrochloride (INN) for use in human medicine.

1.4 "FDA" means the U.S. Food and Drug Administration or any successor agency.

1.5 "Field" means the prevention of chemotherapy induced nausea and vomiting (CINV) in terms of the Regulatory Authorities approved indication.

1.6 "HHC's Other Distributors" means any distributor and/or licensee appointed by HHC to promote and sell pharmaceutical preparations containing the Compound in any country of the world outside the Territory and outside the Field in the Territory.

1.7 "Improvements" means all improvements, modifications or developments relating to the Field and/or to the Product forms subject of this Agreement, which

might improve the quality or improve consumer acceptance and/or patient compliance of the Products. For clarity, except to the extent MGI has exercised its right of first refusal wider Article 2.6, "Improvements shall not include dosage forms other than the intravenous ("I.V.") formulation as shall be described in the Registration and/or indications other than within the Field.

1.8 "Know-how" means valuable, secret and substantial information regarding the Products in the Field, including but not limited to documentation and information on file with the FDA or other Regulatory Authority in support of the Registration, which may be necessary, useful or advisable to enable MGI to promote, market and sell the Products in the Field in the Territory, as far as controlled by or available to, and not prohibited to be disclosed or licensed by, HHC, all as listed in the First Appendix hereto and as is or will be specified in the documentation which HHC has delivered or will deliver to MGI after execution of this Agreement.

1.9 "Net Sales" means the gross sales in local currencies of all Products said in the Territory by MGI and/or its Affiliates, including any local Affiliate in Canada, for arm's lenghth sales to any non-Affiliated third party less those normal and customary deductions made under Generally Accepted Accounting Principles to are at Product sales. Such deductions shall comprise any trade and quantity discounts, returns and allowances, rebates, cash discounts, sales and excise taxes, transportation and insurance charges, chargebacks and other amounts paid on sale or distribution of Product, provided that such deductions (i) arc directly linked to and related to the gross sales

invoiced amount, (ii) are specifically related to commercial policies having the purpose of acquiring, maintaining and maximising sales and enlarging the market share of the Product, (iii) do not exceed the average usual and customary deductions of this kind for similar products in the Field in the Territory and (iv) shall not include any mark-up or other increase over costs actually incurred by MGI and/or its Affiliates in connection with such gross sales. It is understood that said deductions shall not include any amount related to had or doubtful debts. Where (a) a Product is sold as one of a number of items (bundled transaction) without a separate price; or (h) the consideration for the Product shall include any non-cash element; or (c) the Product shall be transferred in any manner other than an invoiced sale, the Net Sales applicable to the quantity of Product of any such transaction shall be deemed to be the average Net Sales for all other transactions of Product at that time in the Territory.

1.10 "Parties" means HHC and MGI and "Party" means either of them as the context indicates.

1.11 "Patent" means (a) the patents and the patent applications licensed or assigned to HHC pursuant to the Syntex Agreement, as listed in the Second Appendix hereto; (b) all patents in the Territory issuing from said applications; (c) any additions, divisions, continuations, continuations-in-part, amendments, amalgamations, reissues and re-examinations of such applications or patents in the Territory; (d) any confirmation, importation and registration patents thereof in the Territory, and (e) any extensions and renewals of all such patents and patent applications in the Territory in whatever legal form and by whatever legal title they are granted.

1.12 "Products" means the pharmaceutical preparations for human use in I.V. dosage form, containing the Compound as an active ingredient in the formulation that will be described in the Registration and such other formulations for which MGI exercises its right of first refusal pursuant to Article 2.6. The current formulation as submitted to the Food and Drug Administration of the United States of America in the IND 39,797 Amendment # 64 and to the Therapeutic Products Programme of Canada in the IND 9427-H01336-21C is described in the Third Appendix hereto.

1.13 "Registration" means any official approval, or authorization by the competent Regulatory Authority of each country in the Territory, which is legally required to lawfully market the Products in the Territory, including, without limitation, any governmental price approval or reimbursement approved under a national health insurance system.

1.14 "Regulatory Authority" means, with regard to the United States of America the United States Food and Drug Administration (FDA) and, with regard to Canada the Therapeutic Products Programme, or any other agency which shall be responsible for the issuance of the Registration throughout the term of this Agreement.

1.15 "Territory" means the United States of America and its possessions and territories (Puerto Rico, United States Virgin Islands), and Canada and its provinces, possessions and territories.

1.16 "Trademark' means the trademark DEDYS® or ONICIT®, which are and shall be HHC's property, or under another trademark to be selected by the Parties, it being understood that HHC shall bear reasonable

documented expenses in connection with such selection, and which shall be HHC's property.

ARTICLE 2 - GRANT OF RIGHTS AND COMPETITION

2.1 Subject to all terms and conditions of this Agreement, HHC hereby grants MGI, and MGI hereby accepts, an exclusive, non-transferable and non-assignable (except as provided at Article 2.8 here below with regard to distribution, promotion and sale of the Products in the Field by a local Affiliate of MGI in Canada), royalty-bearing license under the Patents and to use the Know-how, to distribute, promote, market and sell the Products in the Territory for the Field.

Moreover, subject to all terms and conditions of this Agreement, HHC hereby grants MGI, which hereby accepts, an exclusive, non-transferable and non-assignable (except as provided at Article 2.8 here below with regard to distribution, promotion and sale of the Products in the Field by a local Affiliate of MGI in Canada), royalty-bearing license to affix the Trademark to the Products and to use it in connection with the distribution, promotion, marketing and sale of the Products in the Territory for the Field,

2.2 The exclusivity granted pursuant to this Article 2 means that only NMI may be licensed by HHC to distribute, promote, market and sell the Products in the Territory for the Field.

The Parties acknowledge, however, that HHC has or may have other licensing arrangements for the Products outside the Territory, or within the Territory outside the Field, and that as a consequence, Products marketed by third parties may enter the Territory or the Field; provided that HHC shall use commercially

reasonably efforts to include in such other arrangements appropriate provisions prohibiting, to the maximum extent permissible under applicable laws and mutations, that such Products marketed by third parties enter the Territory or the Field, and to enforce such provisions as and when necessary. HHC further undertakes to provide MGI, upon MOTs written request, with a copy of such provisions for the purpose of enabling MGI to verify compliance with this Article 2.2.

2.3 MGI agrees not to knowingly market, ship, distribute, promote, sell or otherwise put into circulation the Products outside the Territory and/or outside the Field and to expressly and consistently inform distributors and/or wholesalers for the Products, by warning letters or other appropriate and effective means, that the distribution and sale of the Products outside the Territory and/or outside the Field is prohibited and to enforce such prohibition as and when necessary. In the event that MGI enters into any agreements with its distributors and/or wholesalers for the Products, it shall use commercially reasonable efforts to include in any and all said agreements appropriate provisions prohibiting, to the maximum extent permissible under applicable laws and regulations, that the Products are distributed outside the Territory and/or outside the Field, and to enforce such provisions as and when necessary. Moreover, MGI undertakes to pass on to HHC any request for the Products coming to MGI from any party or for sale outside the Territory,

2.4 MGI agrees not to, directly or indirectly, research, develop, manufacture, register, sell, promote, or distribute in the Territory any competing product throughout the term of this Agreement, except with

the prior written authorization of HHC, which authorization may be withheld by HHC in its sole and absolute discretion. A "competing product" is hereby defined as any anti-emetic pharmaceutical products or therapies having the same indications of the Products.

2.5 MGI acknowledges and agrees that it shall not have the right to manufacture, directly or indirectly, the Compound and/or the Products. In order to maintain at all times the highest quality for the Products and to ensure a scientifically proper and safe exploitation of the licensed Know-how and Patents and in order to maintain and to protect the goodwill of the Trademark, MGI undertakes to purchase of its Products' requirements exclusively from a source indicated or approved by HHC; provided that such source meets all requirements of applicable Regulatory Authorities and specifications for the Products applicable in the Territory.

2.6 The Parties hereby acknowledge and agree that the development and marketing of an oral formulation of the Compound will be useful for enlarging the market of pharmaceutical preparations containing the Compound in the Field and undertake to discuss in good faith on the timing, costs and any other conditions relevant to the development, registration and marketing of such oral formulation. In addition, HHC shall offer to MGI a first negotiation right for the Territory (or some portion thereof) to distribute, promote, market and sell any new dosage form(s) and/or formulation(s) (other than the I.V. formulation as shall be described in the Registration) of the Products in the Field (i) becoming available to HHC throughout the term of this Agreement and which HHC is free to offer in the Territory (or a portion thereof) or (ii) which development and marketing may be deemed of

interest for the Parties or any of them. MGI shall have a two-month time from notification by HHC to exercise said first negotiation right and to decide, by written election to HHC, whether it is interested in said new dosage form(s) and/or formulation(s) or not. If MGI decides to exercise said first negotiation right, it shall do so by notifying HHC in writing. Upon such notice, the Parties shall discuss and seek an agreement in good faith on the best steps to be taken and on the timing and resources needed to develop, file the relevant application for registration and launch said new dosage form(s) and/or formulation(s) in the Territory, as well as on the royalties, supply prices and any other conditions of supply and marketing of said new dosage form(s) and/or formulation(s), including but not limited to relevant minimum sales obligations. Upon reaching said agreement, this Agreement shall be accordingly amended and fully applicable also with respect to such new dosage form(s) and/or formulations(s), which shall be included in the definition of Products hereunder. If MGI decides not to exercise said first negotiation right or if an agreement cannot be reached within b (six) months from the date of MGI's notification of interest to HHC, HHC shall then be free to fully exploit said new dosage form(s) and/or formulation(s) of the products in the Field with any third party in the Territory, however under a trademark different from and not confusingly similar to the Trademark and provided that HHC shall not offer to such third parties, taking into account all circumstances of the proposed transaction, business conditions which are better than those offered to MGI in connection with said new dosage form(s) and/or formulation(s) and provided further that such exploitation does not conflict with, or otherwise violate the terms and conditions of this Agreement.

2.7 MGI acknowledges that there are or there may be different uses or indications of the Products and that the rights and licenses hereby granted by HHC are limited to the Field. HHC retains the right to, and shall be free to exploit at its own discretion into and outside the Territory, any and all uses or indications of the Products outside the Field, in whichever dosage form and/or formulation HHC may deem fit, including but not limited to I.V., and MGI shall have no rights in any respect whatsoever to such uses and/or indications outside the Field, provided that HHC shall not be entitled to use the Trademark or trademarks which are confusingly similar to the Trademark in respect of marketing and sale in the Territory of said uses and/or indications of the Products outside the Field; provided that such exploitation does not conflict with, or otherwise violate the terms and conditions of this Agreement.

2.8 MGI shall not have the right to sublicense or otherwise transfer any of its rights and/or obligations hereunder; provided that MGI shall be entitled to engage en-promotion partners in the United States, subject to HHC's prior approval, not to he unreasonably withheld. Moreover, MGI shall not have the right to sub-contract any of its rights and/or obligations hereunder, provided however that MGI shall be entitled to have the logistics and warehousing activities (excluding however invoicing and billing to customers) relevant to the Products carried out by its Affiliates or by third parties in the Territory. It is understood that MGI shall have the right to have the Products distributed, promoted and sold in Canada by its local Affiliate, whose name and address, and any change thereof, shall be timely notified to HHC.

MGI undertakes and warrants that its Affiliate in Canada shall strictly comply with MGI's applicable obligations and warranties stated in this Agreement and any breach of such obligations and/or warranties by such Affiliate shall he regarded in all respects and in particular for the purposes of Articles 11 and 17 hereunder, as a breach by MGI. Correspondingly, MGI shall be fully responsible towards HHC for any action and/or omission of its said Affiliate, and shall defend, indemnify and keep HHC wholly free and harmless from any connected claims, damages, liabilities, losses, costs and/or expenses. Moreover, MGI expressly undertakes and warrants that any agreement with respect to the Products between itself and its Affiliate in Canada shall be fully consistent with this Agreement and undertakes to send to HHC, upon HHC's written request, a copy of any said executed agreement (with economic terms redacted) for the purpose of enabling HHC to verify compliance with terms and conditions hereof.

MGI shall be permitted to disclose to its Affiliate in Canada such Know-how and other relevant information to the extent strictly necessary and appropriate to correctly carry out its obligations hereunder, provided however that any such disclosure shall be made only under a confidentiality agreement, for the benefit of and approved in writing by HHC, having terms at least as restrictive as those provided herein.

2.9 MGI shall not enter into any agreement with third parties with respect to the Compound and/or the Products, except as may be necessary for the purpose of a full and collect exploitation of the Products in accordance with all terms and conditions of this Agreement. Upon FMC's written request, MGI shall send to HHC a copy of any said executed agreement

(with economic terms redacted) for the purpose of enabling HHC to verify compliance with terms and conditions hereof. Nothing in this Agreement shall be construed as giving MGI any right to use or otherwise deal with the Know-how, the Patents and/or any other information received hereunder for purposes other than those of distributing, promoting, marketing and selling the Products in the Territory for the Field in accordance with the terms and conditions of this Agreement. In particular, and without limiting the generality of the foregoing, MGI hereby undertakes not to file any application for the Registration of generics of the Products in the Territory or outside the Territory throughout the term of this Agreement.

2.10 MGI shall promptly inform HHC of any misappropriation, or threatened or presumed misappropriation of the Know-how winch comes to its attention. HHC will decide on the steps to be taken after having discussed the case with MGI and MGI shall assist, bearing exclusively its own internal costs and HHC bearing MGI's reasonable out-of-pocket costs, HHC in taking legal action, if deemed necessary by HHC, against such misappropriation.

2.11 Each Party shall promptly and fully inform the other if it has a reasonable basis to believe that there have been unauthorized sales of the Products into or outside the Territory, and shall use practical efforts with all such persons to act consistently with the terms and conditions of this Agreement.

2.12 In the event that MGI fails to respect the limitations of the licenses granted under this Article 2 and MGI or its Canadian Affiliate knowingly distributes Products outside the Territory and/or outside the Field, or fails to enforce appropriate prohibitions on such distribution of Products outside the Territory

and/or outside the Field by its distributors and/or wholesalers in accordance with Article 2.3 here above, MGI shall be deemed to be in material default, and HHC shall have the right, in its sole discretion, to terminate this Agreement by written notice to MGI, which breach is not cured within a sixty (60) days notice period.

ARTICLE 3 - EXCHANGE OF INFORMATION AND IMPROVEMENTS

3.1 Throughout the term of this Agreement, HHC shall supply MGI in writing and free of charge with any relevant Know-how, in addition to that already supplied at the Effective Date hereof, which may be or become available to HHC and which HHC is free to disclose. Notwithstanding the foregoing, nothing in this Agreement shall require HHC to obtain additional Know-how from third parties.

In the event that MGI should require technical assistance in connection with its initial sale of the Products in the Territory, HHC will use its commercially reasonable efforts to assist MGI for reasonable periods of time and at times convenient to HHC.

3.2 MGI shall supply HHC in writing or by any other appropriate support, free of charge, with any and all technical and/or scientific information and data relating to the Products and/or the Compound, as soon as they are or become available to MGI throughout the term of this Agreement. MGI shall communicate any such information and data to HHC and MGI shall use such information and data for the purpose of the distribution, promotion and sale of the Products in the Territory for the Field in accordance with the terms and conditions of this Agreement. HHC shall have the right to use such information and data for the purpose

of its business and to disclose the same to HHC's Affiliates and to HHC's Other Distributors, which in turn shall have the right to use them for the purpose of the distribution, promotion and sale of pharmaceutical preparations containing the Compound outside the Territory and outside the Field in the Territory.

3.3 MGI's rights hereunder shall include any Improvement carried out by or which may he discovered, developed, invented or acquired by HHC, for use in accordance with the terms and conditions of this Agreement.

Any Improvement which may be carried out by or which may he discovered, developed, invented or acquired by MGI, its officers, agents or employees, may be used by MGI for the purpose of the distribution, promotion and sale of the Products in the Territory for the Field in accordance with the terms and conditions of this Agreement and will be promptly disclosed and is hereby automatically licensed free of charge to HHC on an exclusive basis even as to MGI (except for those MGI's activities described here above) and HHC shall have the right to sublicense the above Improvements to HHC's Affiliates and to HHC's Other Distributors for use outside the Territory and outside the Field in the Territory. MGI shall not incur any obligation to any third party which may prohibit or impair its ability to disclose and license Improvements to HHC.

3.4 All Know-how, Improvements and/or other information and data disclosed to MGI hereunder arc at all times and shalt after expiration or termination of this Agreement for any reason remain HHC's sole and exclusive property.

ARTICLE 4 - DEVELOPMENT AND REGISTRATION OF PRODUCTS

4.1 MGI hereby acknowledges and agrees that

4.1.1 at the Effective Date of this Agreement the Products are under development by HHC for the purpose of submitting the relevant Registration application to the Regulatory Authorities of the Territory,

4.1.2 the development of the Products by HHC may be interrupted or discontinued by HHC as set forth in Article 4.2, if said development becomes commercially unreasonable, or the relevant results may be negative or unfavorable,

4.1.3 the development work presently carried out will not necessarily result in the grant of the Registration of the Products and

4.1.4 HHC makes no warranty and nothing in this Agreement may or shall be construed as a warranty by HHC that the Products will obtain the Registration or that a Product can be developed and registered from the Know-how and MGI shall have no claim against HHC arising out of any delay or refusal by the Regulatory Authorities to issue the Registration in any way whatsoever.

4.2 HHC will use commercially reasonable efforts to complete the development of the Products in accordance with the Development Chart attached as Fourth Appendix hereto and, subject to satisfactory development of the Products and provided that no unforeseeable events occur or additional requests are made by the Regulatory Authorities with respect to the development of the Products described in the Development Chart hereto attached, to file the NDA for the Products in the United States of America not later

than 31 December 2002. For the avoidance of doubt, nothing in this Agreement shall require HHC to perform additional testing or additional development work other than as described in the Development Chart attached hereto. In the event the development of the Products is interrupted or discontinued by HHC or the relevant results are negative or unfavorable as mentioned at Article 4.1.2 here above or in the event the Registration of the Products is not granted as mentioned at Article 4.1.3 here above, the Parties shall meet to discuss and seek an agreement in good faith on such additional clinical trials and other development activities as the Parties may deem appropriate and commercially reasonable, including the direct performance and funding by MGI of the further development activities deemed necessary for the registration of the Products, in which case (i) all relevant protocols shall have to be previously discussed with and approved in writing by HHC, (ii) data, information and results arising from said further development shall be the exclusive property of HHC and MGI shall have the right to use them in connection with the distribution, promotion and sale of the Product in the Territory for the Field, (iii) external documented costs and expenses incurred by MGI with third parties in connection with said further development shall be credited by HHC to MGI against payment of royalties on Net Sales as per Article 7.3 here above (provided that in each Accounting Period the sum to be credited to MGI shall not exceed fifty percent of the royalties which would be payable by MGI in respect of said Accounting Period). If such an agreement cannot be reached within six months from beginning of discussions in this regard, then this Agreement shall automatically terminate, and Articles 17.6. 17.7 and 17.8 hereunder shall apply, it being

understood that HHC shall have no obligation, liability or responsibility whatsoever to compensate, indemnify or reimburse MGI for any payments, damages, losses, costs or expenses incurred by MGI in connection with this Agreement or termination hereof and that the payments already effected by MCA at the effective date of termination pursuant to Article 7 hereunder shall be retained by HHC.

4.3 Applications for the Registration in the Territory shall be filed by HHC in its own name and at its own expenses. HHC shall also pay all administrative fees for the maintenance in force of the Registration throughout the term of this Agreement.

4.4 MGI expressly acknowledges and agrees that HHC is and shall at all times remain the sole and exclusive owner of the Registrations and that ownership of said Registrations and any and all rights, title and interest (including any accompanying goodwill) are, and shall at all times remain, vested in HHC.

4.5 After approval of the NDA for the Products in the United States and compliance by MGI with the provision of Article 7.1.5 hereunder, MGI shall be appointed by HHC as HHC agent with respect to the NDA for the Products in the Field ("FDA Agent) and shall manage and carry out on behalf of HHC all relevant communications and relations with the FDA. in addition, MGI shall be entitled to participate in all negotiations and discussions between HHC and the FDA regarding any labeling for the Products in the Field and shall perform and carry out all post-Registration activities, requested by the FDA, connected with the NDA For the Products in the Field with the exception of those activities specifically listed in the Fifth Appendix hereto, which shall be performed and carried out by HHC. Nothing in this Agreement

precludes HHC from appointing an FDA Agent on different NDAs for products other than the Products (including, without limitation, any new dosage form(s) and/or formulation(s) of the Products in the Field under the terms provided at Article 2.6 hereabove) or for the Products outside the Field or from changing HHC's corporate agent in the United States ("U.S. Agent") at any time.

All said activities, communications and relations as well as MGI's role of HHC's FDA Agent as described above shall be performed by MGI in close coordination with HHC, directly or through third parties, as the holder of the Registrations. In particular, MGI shall copy within 48 hours and keep HHC fully and promptly informed, throughout the term of this Agreement, of all communications received from the Regulatory Authorities of the Territory concerning the Products and/or the Compound. Without prejudice to full compliance by both Parties with any obligations established by applicable laws and regulations of the Territory with regard to adverse events reporting and any other deadlines set by Regulatory Authorities, any and all communications to Regulatory Authorities relevant to the Compound and/or the Products and connected with the activities described above, shall be sent by MGI only after the relevant contents have been discussed with and approved in writing by HHC, which approval shall be deemed to have been given if HHC does not otherwise respond within ten working days in Switzerland of receipt of such proposed communication; provided however, that MGI shall not he required to obtain such prior approval with respect to those mutually agreed routine administrative communications with the FDA. MGI further undertakes and warrants that it shall at all times strictly comply with any and all laws, rules and regulatory requirements in

force in the Territory in connection with the activities, communications and relations contemplated herein.

4.6 MGI shall store and distribute, and shall cause the Products to be stored and distributed according to applicable current Good Manufacturing Practice or any other applicable laws and regulations. MGI shall permit HHC's representatives, during normal business hours and upon three business days advance notice in writing, to inspect those areas of the warehouses of MGI, its Affiliates and distributors where the Products are stored, for the purpose of verifying compliance with applicable laws and regulations as well as with this Agreement

4.7 If material alterations, modifications or amendments of this Agreement or of the Products are imposed by any Regulatory Authority as prerequisites for the grant or the continuation of the Registration of any of the Products, or if Registration of any of the Products is suspended or withdrawn by any said Regulatory Authority, each Party shall notify the other promptly after receipt of notification from such Regulatory Authority and the Parties shall endeavor to agree upon a reasonable and mutually acceptable resolution thereof In the event that the Parties are unable to agree upon such a resolution, HHC shall have the right at its sole discretion, upon written notice to MGI, to delete the Product or Products in question from this Agreement or to take any other measure which it reasonably deems necessary or advisable and, if necessary, to terminate this Agreement, in which case the consequences provided for at Article 17.6, 17.7 and 17.8 hereunder shall apply, it being understood that in any case, except as expressly provided in Article 11 of this Agreement, HHC shall

have no obligation, liability or responsibility whatsoever to compensate, indemnify or reimburse MGI for any payments, damages, losses, costs or expenses incurred by MGI in connection with this Agreement or termination hereof and that the payments already effected by MGI at the effective date of termination pursuant to Article 7 hereunder shall be retained by HHC.

4.8 MGI shall collaborate with and assist HHC and/or any of HHC's Other Distributors for the purpose of obtaining Registrations outside the Territory and/or, outside the Field in the Territory. Such collaboration and assistance shall include, but not be limited to, doing all such acts as may be required by HHC for the purpose of permitting access and maximum use by HHC and/or HHC's Other Distributors of the documentation and results of the activities described at Article 4.5 hereabove and of development work on the Products carried out by MGI pursuant to Article 5.3 here below. HHC shall reimburse MGI for reasonable out-of-pocket expenses incurred in providing such collaboration and access.

4.9 Each Party undertakes to give the other Party Full, accurate and prompt information in writing with regard to adverse events associated with the use of the Products, whether or not ascertained to be definitely attributable to the Products or the Compound, in strict accordance with the procedures and rules established in the Sixth Appendix attached to this Agreement.

4.10 In the event of a recall, complaint, field alert, product withdrawal relevant to the Products marketed by MGI in the Territory, the Parties shall strictly follow the procedures and rules established in the Seventh Appendix to this Agreement.

4.11 MGI shall permit HHC and/or any authorized representative or consultant of HHC to enter MGI's premises, as well as the premises of MGI's Affiliates and/or distributors in the Territory, during normal business hours and upon at least three (3) business days advance notice, to audit and verify compliance by MGI, its Affiliates and distributors with regulatory and other requirements in force in the Territory, as well as with this Agreement, with respect to all aspects related to Registration and to correct and safe distribution, promotion, marketing and sale of the Products in the Territory or in connection with any recall contemplated by Article 4.10 hereabove.

Such audit shall include, without limitation, the right to examine any internal procedures or records of MGI, its Affiliates and distributors relating to the Products. MGI shall give and shall cause its Affiliates and distributors to give, all necessary assistance for a full and correct carrying out of the audit by HHC. No such monitor and/or audit by HHC shall relieve MGI, its Affiliates and distributors of any of their obligations under this Agreement in any way whatsoever.

In the event that any Regulatory Authority or any other competent authority of the Territory carries out or gives notice of its intention to carry out any inspection or audit of MGI, its Affiliates or distributors or otherwise takes any action in relation to the Products, MGI shall immediately notify HHC in full details and shall use commercially reasonable efforts to insure that HHC shall have the right to be present at and to participate in any such inspection or audit.

ARTICLE 5 - POST-REGISTRATION DEVELOPMENT

5.1 HHC shall use commercially reasonable efforts to provide any further clinical and product development that may be requested by any Regulatory Authority in the Territory for the maintenance of the Registration.

to market Products more effectively in the territory.

5.3 MGI shall not undertake nor carry out any trial relevant to the Products without the prior written approval of HHC. MGI shall perform and fund any trials mentioned at article 52 hereabove in accordance with a development plan to be agreed upon in advance with HHC. All relevant protocols shall have to be discussed and approved in writing by HHC. Any and all data, information and know-how, whether patentable or not, arising from said trial will be promptly disclosed and is hereby automatically licensed free of charge to HHC on an exclusive basis even as to MGI (provided that MGI shall have the right to use such data, information and know-how solely for the purpose of the distribution, promotion and sale of the Products in the Territory for the Field in accordance with the terms and conditions of this Agreement) and HHC shall have the right to sublicense said data, information and know-how to HHC's Affiliates and to HHC's Other Distributors for use outside the Territory and outside the Field in the Territory. MGI shall not incur any obligation to any third party which may prohibit or impair its ability to disclose and license said data, information and know-how to HHC. In addition, HHC shall use commercially reasonable efforts to put at MGI's disposal for use in the distribution, promotion, marketing and sale of the Products in the Territory for the Field in accordance

with the terms and conditions of this Agreement, any post-registration trial carried out by HHC's Other Distributors with regard to the Products.

ARTICLE 6 - TRADEMARK OF PRODUCTS

6.1 The Products shall he distributed, promoted, marketed and sold by MGI in the Territory exclusively under the Trademark.

6.2 MGI shall use the Trademark exclusively in connection with and for the purpose of the distribution, promotion, marketing and sale of the Products for the Field in the Territory. MGI acknowledges that it shall be entitled to no rights whatsoever in the Trademark except as is specifically granted pursuant to this Agreement and then only to the extent of the express grant.

6.3 HHC shall register MGI, and MGI shall assist HHC in having MGI registered, as a licensee in the Trademark Register of the Territory as necessary and useful, in particular regarding the recordation as "Registered User" where corresponding legal provisions exist. Such registration shall be cancelled after expiration or termination of this Agreement for any reason upon the request of HHC.

6.4 HHC's trade name and logo shall appear on all Products packaging, labels and inserts and other materials which MGI uses for the distribution, promotion, marketing and sale of the Products in such form and manner as shall he approved by HHC in writing in compliance with all requirements of applicable Regulatory Authorities.

6.5 MGI shall make no use of the Trademark except in the form and with the graphics authorized in advance by HHC. MGI shall for each use feature a

prominent notice and acknowledgement of the registered Trademark ownership and license by WIC in conjunction with all usage of the Trademark. HHC shall have the right to review and approve all intended uses of the Trademark in any packaging, inserts, labels, promotional or other materials relating to the Products prior to actual use thereof.

6.6 MGI will not alter, obscure, remove, conceal or otherwise interfere with any markings, names, labels or other indications of the source of origin of the Products which may be placed by HHC on the Products.

6.7 MGI will not use nor apply for registration of any trademark, trade-name or logo in connection with the Products, nor shall it use or apply for registration of any trademark, logo or design which includes the Trademark, atone or in combination, in or outside the Territory, without the prior written authorization of HHC, which authorization HHC may withhold in its sole and absolute discretion.

6.8 Nothing contained in this Agreement shall be construed as giving MGI a right to use the Trademark or portions thereof or any word confusingly similar to the Trademark or the name "Helsinn" as MGI's corporate name or any part thereof. Throughout the term of this Agreement and thereafter, MGI shall not use nor apply for registration of, any mark, logo or design, in or outside the Territory, which is, or is likely to be, confusingly similar to, or could cause deception or mistake with respect to, the Trademark or to the name "Helsinn" on any pharmaceutical or chemical or healthcare product or service.

6.9 Nothing contained in this Agreement shall be construed as giving MGI the right to use the Trademark outside the Territory or for any other product than the Products and HHC may use, or license others to use, the Trademark in all jurisdictions outside the Territory.

6.10 The Trademark shall always be used together with the sign "R" or the sign "TM" or such other customary symbol or legend which identifies correctly the status of the Trademark.

6.11 MGI recognizes the exclusive rights of HHC regarding the Trademark and acknowledges that it shall not acquire any rights in respect of the Trademark of HHC in relation to the

6.12 HHC shall keep in force the Trademark by paying the necessary fees throughout the term of this Agreement and by using all reasonable efforts to defend any action or proceeding for cancellation of the Trademark, bearing the whole cost thereof and MGI shall render any reasonable assistance in this respect.

6.13 MGI shall promptly notify HHC of any threatened or presumed significant counterfeits, copies, imitations, simulations of, or infringement upon, the Trademark or the name "Helsinn" or of any other act of unfair competition which comes to its attention. HHC will decide on the steps to be taken after having discussed the case with MGI and MGI shall give its full co-operation therefor at HHC's expense. Should it occur that HHC for any reason decides not to defend the Trademark, then MGI shall have the right to take appropriate action for defending the Trademark in its own name with the consent of HHC. In such case, MGI shall bear all the costs and shall be entitled to retain any compensation paid by third persons in this respect

6.14 MGI acknowledges that HHC has no adequate remedy under this Agreement or at law in the event that MGI were to use the Trademark in a manner not authorized by this Agreement and that HHC would, in such circumstances, be entitled to specific performance, injunctive or other equitable relief, including interlocutory and preliminary injunctive relief.

6.15 MGI shall be entitled to mark the Products packaging, labels and inserts with the MGI name and logo, in a manner reasonably acceptable to HHC.

ARTICLE 7 - COMPENSATIONS BY MGI

7.1 As consideration for the right granted and information disclosed under this Agreement, in addition to the amount of USD5,000,000 (United States Dollars five million) which has been paid by MGI to HHC in accordance with the Letter of Intent mentioned at recital (d) here above, MGI shall pay to HHC, upon occurrence of the following events, the following milestone payments, which shall not be refundable nor creditable towards future royalties:

7.1.1 At signature of this Agreement MGI shall pay to HHC USD6,000,000 (United States Dollars six million), of which up to 50% may, at MGI's option, be paid in freely tradable shares of MGI common stock as better specified at Article 7.2 hereunder;

7.1.2 Six months after execution of this Agreement, MGI shall pay to HHC USD2,000,000 (United States Dollars two million);

7.1.3 At Type B pre-NDA meeting with the FDA, MGI shall pay to HHC USD4,000,000 (United States Dollars four million);

7.1.4 At NDA filing in the United States of America, MGI shall pay to HHC USD10,000,000

(United States Dollars ten million) of which up to 50% may, at MGI's option, be paid in freely tradable shares of MGI common stock as better specified at Article 7.2 hereunder,

7.1.5 At NDA approval in the United States of America, MGI shall pay to HHC USD 11,000,000 (eleven million).

The above milestone payments shall be paid by MGI to HHC by wire transfer of immediately available funds to an account designated in writing by HHC; provided that the payments described at Articles 7.1.2 and 7.1.3 shall be paid pursuant to the terms of an Escrow Agreement among the Parties and U.S. Bank Trust Association in the form attached as Appendix 8 hereto, dated as of the Effective Date hereof. The milestone payments described at Articles 7.1.1, 7.1.2, 7.1.3, 7.1.4 and 7.1.5 shall be paid within 15 (fifteen) days of occurrence of the relevant event. Failure to pay any of the milestones on a timely basis shall entitle HHC to terminate this Agreement if MGI fails to cure such breach within a 15 (fifteen) days notice period.

7.2 MGI agrees to promptly inform HHC in writing as soon as it elects to effect part of the milestone payments under Articles 7.1.1 and 7.1.4 hereabove in freely tradable shares of MGI common stock. In this case, MGI shall issue to HHC such number of freely tradable shares of MGI common stock calculated by dividing the amount to be paid in MGI common stock by the average of the closing prices for such MGI common stock (as reported in The Wall Street Journal or, if not reported therein, in another mutually agreed upon authoritative source) for the 30 (thirty) trading days before the date of payment of the related milestone payment (the "Original Price"). MGI shall deliver the certificate representing such shares to

HHC by overnight courier within five (5) business days after such date of payment. Such shares shall be duly authorized, validly issued, fully paid and non-assessable and shall he free and clear of any and all liens, claims or other encumbrances. Notwithstanding anything contained herein to the contrary, MGI shall not be entitled to elect to satisfy its payment obligation under Articles 7.1.1 or 7.1.4, as the case may be, in freely tradable shares of MGI common stock, if, at the time that the payment becomes due pursuant to Article 7.1.1 or Article 7.1.4 above, as the case may be, the Continued Listing - Standard 2. HHC acknowledges that any shares received from MGI in payment of its milestone payment obligations under Articles 7.1 or 7.1.4 of this Agreement will be "restricted securities" within the meaning of Rule 144 under the U.S. Securities Act of 1933, and that such shares will not be transferable in the U.S. markets unless and until such shares are either registered under the U.S. Securities Act of 1933 or an exemption from such registration requirement is available. MGI agrees that, unless a registration statement enabling such shares to be freely tradable by HHC upon receipt has been filed by MGI and declared effective by the U.S. Securities and Exchange Commission and HHC has received reasonable assurances that MGI will maintain the effectiveness of such registration statement until HHC fully liquidates such shares in accordance with the restrictions contained in the last sentence of this Article 7.2, in each case prior to the date of delivery of such shares, then MGI shall not be entitled to elect to make part of the milestone payment under Articles 7.1.1 or 7.1.4 in shares of MGI common stock. MGI and HHC hereby acknowledge that, in connection with any such registration of shares of MGI common stock, MGI and HHC will use their

reasonable best efforts to negotiate in good faith a registration rights agreement for such registration on terms reasonable and customary for such agreements. MGI agrees that, if and to the extent that HHC sells any shares of MGI common stock received hereunder on the NASDAQ/NMS (or on any securities exchange or other public trading market on which MGI's common stock is then traded) at a price (the "Sale Price") that is less than the Original Price applicable to those shares, then MGI shall make a cash payment to HHC in United States Dollars equal to the difference between the applicable Original Price and the Sale Price, multiplied by the number of shares sold by HHC at that Sale Price; provided, however, that MGI's obligation to make such payments shall terminate and not apply to any sale of shares by HHC occurring after the day on which, assuming HHC were selling as many shares as possible each day subject to the volume limitations described hereunder in this Article 7.2, HHC could have disposed of all of its shares in such market. MGI shall pay such amount via wire transfer of same day funds within five days after receipt from HHC of evidence of such sale reasonably satisfactory to MGI Notwithstanding the filing and effectiveness of such registration statement, HHC agrees that, in connection with any sale of such MGI shares on the NASDAQ/NMS (or on any securities exchange or other public trading market on which MGI common stock is then traded), the number of shares of MGI common stock sold by HHC on any day will not exceed 10% (ten percent) of the average daily trading volume of MGI common stock in that market for the five trading day period ending two trading days prior to the date of such sale; provided, however, that (i) any shares sold by "HHC in one or more block sales of at least 20,000 shares each which are effected

through a market maker for MGI common stock shall not be counted for purposes of the foregoing volume limitations, and (ii) such volume limitations shall however not apply to the extent that they require HHC a period longer than 90 (ninety) days from the first sale of MGI's shares by HHC to sell MGI's shares.

7.3 In addition to the above milestone payments, MGI shall pay running royalties as follows:

7.3.1 in consideration of the license granted hereunder on the Know-how, MGI shall pay to HHC or HHC's nominee a royalty of 3% (three percent) on all Net Sales throughout the term of this Agreement. It is expressly agreed that in case the Know-how becomes publicly known other than by action of HHC, the above royalty shall continue to be payable throughout the term of this Agreement, without prejudice to the payment to HHC of additional damages in case the Know-how becomes publicly known by the action of MGI.

7.3.2 In consideration of the license granted hereunder on the Patents, MGI shall pay to HHC or HHC's nominee a royalty of 2% (two percent) on all Net Sales until expiration of all said Patents, on a county-by-country basis.

7.3.3 In consideration of the license granted hereunder on the Trademark, MGI shall pay to HHC a royalty of 3% (three percent) on all Net Sales throughout the term of this Agreement.

7.3.4 Royalties due by MGI pursuant to this Article shall accrue in United States Dollars (with regard to sales in the United States of America) and in Canadian Dollars (with regard to sales in Canada) and payments shall be made by wire transfer of immediately available funds to an account designated in

writing by HHC in United Slates Dollars (or in Canadian Dollars, as applicable) within 30 (thirty) days after the end of each Accounting Period, in respect of the Net Sales achieved in that Accounting Period. Without prejudice to HHC's right to be paid in accordance with the provisions hereof as well as to any other remedy which may be available to HHC in accordance with this Agreement and/or applicable law, late payments shall bear interests at the prime rate applicable in Switzerland as of the date such payment was originally due.

7.3.5 For the purpose of computing the volume of the Net Sales, the Products shall be deemed to have been sold by MGI or its Affiliates as mentioned at Article 2.8 hereabove on the date of invoicing or on the date of delivering, whichever is first to

7.3.6 Notwithstanding anything contained in this Agreement, during the term of this Agreement MGI shall effect an annual minimum payment equal to 7% (seven percent) of the minimum annual sales established in the Ninth Appendix hereto but only to the extent that the amount so payable annually is greater than the overall amount that would otherwise be payable by MGI pursuant to Articles 7.3.1, 7.3.2 and 7.3.3 above. In the event that MGI does not effect said minimum annual payment within 31st January of the following year throughout the term of this Agreement, HHC shall have the right to terminate this Agreement as set forth in Article 17.4 below.

7.3.7 MGI will add Value Added Tax (VAT) if any, as and where provided by law, to all the royalty accounts rendered and pay such VAT directly to the competent authorities under its own responsibility, or, where so provided by law, mark the royalty accounts

with the notice: "VAT zero rated", stating the title of the exemption or exclusion.

7.3.8 If any official authorization shall be required to enable MGI to effect any payments of compensations due and payable hereunder, MGI shall use its best efforts to secure such authorization within the times stipulated in this Article, and in the event that by reason of such authorization not having been granted the payment is delayed beyond the times so stipulated, MGI shall so advise HHC and shall effect payment by any other lawful means indicated by HHC; failing such indications, MGI shall effect payment within 15 (fifteen) days of such authorization being granted.

7.4 All payments lo be made pursuant to this Agreement represent actual amounts that HHC is entitled to receive and shall not be subject to any deduction for any reason whatsoever. In the event that such payments become subject to duties, taxes or charges of whatever kind or nature (excluding taxes am HHC"s income), such payments shall be increased to such an extent as to allow HHC to receive the net amounts due under this Agreement.

7.5 MGI shall in no case be entitled to off set or otherwise withhold any payment due to HHC hereunder in view of possible, justified or unjustified, claims against HHC.

7.6 If there exists a tax treaty to avoid double taxation between Switzerland and the Territory which reduces the standard rate of withholding tax, MGI shall assist HHC in obtaining the necessary exemption of the withholding tax according to such treaty. Upon submission by HHC of adequate exemption forms or equivalent, if required, MGI shall deduct only

such reduced withholding tax from its payments to HHC and shall submit to HHC the corresponding receipts so that HHC may collect these amounts from its own tax authorities as a tax credit.

ARTICLE 8 - MARKETING AND SALE OF PRODUCTS

8.1 MGI hereby undertakes that it will launch the Products in the Field onto the whole market of each country of the Territory as soon as possible and in any case no later than 6 (six) months from respective Registration and availability of the necessary commercial supply, and that it shall promptly communicate in writing the relevant launching dates to HHC.

8.2 MGI shall be entitled to resell the Products to its customers in the Territory at such prices as it may determine subject to all applicable laws of the Territory. MGI shall keep HHC fully and timely informed on the price of the Products in the Territory and shall promptly notify any change thereof.

8.3 MGI hereby undertakes and warrants that it shall distribute, promote, market and sell the Products throughout the Territory under its corporate name and responsibility and at its own expense. MGI also undertakes and warrants that distribution, promotion, marketing and sale of the Products in the Territory shall fully comply with all laws, regulations and requirements at any time being in force in the Territory and shall be fully consistent with the conditions and requirements of the Registration.

8.4 Marketing, advertising and promotional materials concerning the Products and training manuals for MGI's medical representatives shall be developed and prepared by MGI at its own expense and in coordination with HHC, which shall render reasonable

assistance in this respect. HHC shall have the right to review and approve the final draft of any said material in advance of print thereof, for the purpose of ensuring compliance of said materials with the international profile and marketing strategy of the Product and the Compound, provided that approval by HHC shall be deemed to have been given if HHC does not otherwise respond within ten working days in Switzerland of receipt of such materials.

8.5 MGI shall promote and distribute the Products in accordance with the Product profile and positioning reviewed with HHC and shall regularly supply HHC not later than September 30 in each year throughout the term of this Agreement with its marketing and promotion plans which shall be discussed in good faith with HHC and shall have to be approved in writing by HHC, which approval shall not be unreasonably withheld or delayed. A marketing strategy for the Products shall he developed and prepared by MGI consistent with the Registration and with the international profile of the Products as established by HHC. MGI shall keep HHC informed on all its promotional and marketing activities in the Territory regarding the Products and periodic meetings shall be organized between the Parties in order to discuss any and all aspects relevant to the promotion and marketing of the Products in the Territory.

8.6 MGI shall promptly supply HHC free of charge with original copies, in accordance with HHC's reasonable requests, of all marketing, advertising and promotional materials relevant to the Products and of the training manuals for its medical representatives and subject to Article 14.5, HHC shall be free to use, directly or indirectly, any such material for its business inside the Field outside the Territory. In no

event shall HHC have the right to use such material in the Territory whether inside or outside the Field.

8.7 MGI undertakes to fully develop and pursue the market for the Product in the Field throughout the Territory. Throughout the term of this Agreement, MGI shall, at its own expense, maintain an active sales organization for marketing and selling the Products in the Field throughout the Territory, maintain an adequate and representative stock of the Products to meet market demand in the Territory and undertakes to effectively distribute, advertise, market, sell and promote the sale and use of the Products in the Field throughout the Territory. In particular, and without limiting the generality of the foregoing obligations, MGI shall perform at least the promotion and marketing activities described in the Tenth Appendix hereto and shall secure annual minimum sales of the Products corresponding, in each of the 5 (five) years starting from the second year from launch, as least to 85% (eighty-five percent) of MGI's unit sales base forecast for said year with regard to the United States of America, which is enclosed in the Ninth Appendix to this Agreement. Prior to the expiration of the fourth year of such sates base forecast, the Parties shall discuss in good faith and seek an agreement an annual minimum sales in the United States of America for the remaining term of this Agreement. If such an agreement cannot be reached within the above deadline, then annual minimum sales for the remaining term of this Agreement shall correspond at least to 85% (eighty-five percent) of MGI's unit salts base forecast for said years with regard to the United States of America, which is enclosed in the Ninth Appendix to this Agreement Minimum sales levels with regard to Canada shall be discussed in good faith

by the Parties after a final decision has been made by HHC on the Registration of the Product in Canada.

8.8 MGI shall, within September 30th in each year throughout the term of this Agreement, provide HHC with an annual sales forecast in units for each of the Products. It is also agreed that MGI shall develop and supply HHC with sales forecast for 3 (three) years, starting from the date of Registration and revised annually.

8.9 MGI shall make clear in all dealings with its customers and prospective customers that it is acting as licensee and distributor of the Products and not as agent of HHC.

8.10 The final package of the Products, as well as any change thereof, shall be discussed in good faith and mutually agreed by the Parties and shall comply with all requirements of applicable Regulatory Authorities.

8.11 All packaging, insert sheets, labels, advertising and other materials relevant to the Products shall bear the notice "Distributed under license from Heisinn Healthcare SA, Switzerland", in such form and manner as HHC may deem appropriate subject to any applicable regulatory requirements in the Territory.

ARTICLE 9 - RECORDS AND REPORTS

9.1 MGI shall submit to HHC together with each royalty payment a written royalty statement signed by a responsible officer of MGI which shall show the units of Products sold or otherwise disposed of by MGI, the unit price, the gross sales and the Net Sales of each of the Products, its stock of Products, the quantity of distributed free medical samples, a detailed listing and appropriate evidence and rationale of any and all

discounts granted for each client, wholesaler and/or distributor and any other relevant information in sufficient detail to permit to HHC to determine and verify the royalties due to HHC. Throughout the term of this Agreement and for a period of at least 3 (three) years thereafter, MGI shall keep complete and accurate books, records and accounts in accordance with sound accounting practice covering all its operations hereunder as necessary to determine and verify the units of Products sold or otherwise disposed of by MGI, the gross sales and the Net Sales and the amount of royalties due to HHC. HHC shall have the right, at any time throughout the term of this Agreement and for a period of three years thereafter, during normal business hours and upon at least three (3) business days advance notice, to have such books, records and accounts inspected and audited by its duly authorized representatives or, at HHCs discretion, by an independent certified public accountant to be nominated by HHC and reasonably acceptable to MGI. MGI shall fully co-operate with HHC, its authorized representatives or independent certified public accountant and make available all work papers and other information reasonably requested in connection herewith. In the event the inspection or audit reveals that MGI's reports are not in accordance with actual sales and that an underpayment has occurred, MGI shall immediately pay to HHC any underpaid royalties within 10 (ten) days of the date HHC delivers to MGI the relevant inspection or audit report In case of an underpayment of at least five percent (5%) of the amounts owing during the audited period, MGI shall also bear all the costs of the inspection or audit and any overdue amounts hereunder shall bear interest at the prime rate applicable in Switzerland as of the date such payment was originally due.

9.2 Within 10 (ten) working days in the United States of America from the end of each month throughout the term of this Agreement, MGI shall supply HHC with a written report showing the units of Products sold and the units of free medical samples distributed during such month in the Territory.

9.3 MGI shall promptly provide HHC with written reports of any importation or sale of any pharmaceutical preparation containing the Compound in the Territory of which MGI has knowledge from any source other than HEM, as well as with any other information which HHC may reasonably request in order to be updated on the market conditions in the Territory.

ARTICLE 10 - REPRESENTATIONS AND WARRANTIES

10.1 HHC hereby represents and warrants to MGI as follows:

10.1.1 HHC has been duly organized and is validly existing as a corporation in good standing under the laws of Switzerland. HHC has the corporate power and authority to enter into this Agreement and to consummate the transactions contemplated by this Agreement.

10.1.2 The execution, delivery and performance of this Agreement, and the consummation of the transactions contemplated by this Agreement, by HHC have been duly and validly authorized by all requisite corporate actions. This Agreement constitutes a legal, valid and binding agreement of HHC enforceable against HHC in accordance with its terms.

10.1.3 The execution, delivery and performance by HHC of this Agreement requires no action by or in

respect of, or consent or approval of, or filing with any Governmental Authority.

10.1.4 The execution, delivery and performance by FDIC of the contemplated transactions do not and will not (A) contravene or conflict with the charter or bylaws of HHC, as applicable, (B) contravene or conflict with or constitute a violation of any provisions of any applicable law binding upon HHC, or (C) constitute a default in any material respect under or give rise to any right of termination, cancellation or acceleration of, or to a loss of any material benefit to which HHC is entitled.

10.1.5 There is no action, suit, investigation or proceeding pending against, or to the knowledge of HHC, threatened against or affecting, HHC before any court, arbitrator or any governmental authority, including but not limited to Regulatory Authorities, that in any manner challenges or seeks to prevent, enjoin, alter or materially delay the contemplated transactions, and, to the knowledge of HHC, there is no reasonably valid basis for any such action, suit investigation or proceeding to be brought.

10.1.6 The persons executing this Agreement on behalf of HHC are duly authorized to do so and by so doing have bound HHC to the terms and conditions of this Agreement.

10.1.7 WIC has received no notice from any of third party licensors that it is in material breach of any of its obligations under the Syntex Agreement, and it is not aware of any material breach of the Syntex Agreement. The Syntex Agreement constitutes a legal, valid and binding agreement of HHC, enforceable against HHC in accordance with its terms.

10.1.8 HHC has licensed sufficient rights to the Patents and Know-how under the Syntex Agreement and, other than the grant of license to third party manufacturers, HHC has not assigned and/or granted licenses to the Patents or Know-how in the Territory for the Field, or entered into any inconsistent prior obligations, to any other person or entity that would restrict or impair the rights granted hereunder to MGI.

10.1.9 To the actual knowledge of HHC, (i) as of the Effective Date hereof the Patents are valid and in full force and (ii) as of the Effective Date hereof it is not aware of any existing or pending patents of third parties which would be infringed by the marketing and sale of the Products in the Field in the Territory in accordance with all terms and conditions of this Agreement.

10.1.10 None of the materials provided to MGI pursuant to its due diligence requests contained any untrue statement of material fact.

10.2 MGI hereby represents and warrants to HHC that:

10.2.1 MGI is a corporation duly incorporated, validly existing and in good standing under the laws of the state of its incorporation and has all corporate powers and all governmental licenses, authorizations, consents and approvals required to carry on its business as now conducted and as contemplated to be conducted in connection with the transactions contemplated by this Agreement (the "Contemplated Transactions"). MGI is duly qualified to do business as a foreign corporation in each jurisdiction where the character of the property owned or leased by it or the nature of its activities (after giving effect to the

Contemplated Transactions) make such qualification necessary to carry on its business except where the failure to so qualify would not have a material adverse effect on MGI.

10.2.2 The execution, delivery and performance by MGI of this Agreement and the consummation by MGI of the Contemplated Transactions are within the corporate powers of MGI, and have been duly authorized by all necessary corporate action on the part of MGI. Each of this Agreement and the Escrow Agreement constitutes a legal, valid and binding agreement of MGI, enforceable against MGI in accordance with its terms.

10.2.3 The execution, delivery and performance by MGI of this Agreement requires no action by or in respect of, or consent or approval of or filing with, any Governmental Authority, other than filings with the SEC in fulfillment of MGI's disclosure obligations under U.S. securities laws.

10.2.4 The execution, delivery and performance by MGI of the Contemplated Transactions do not and will not (A) contravene or conflict with the charter or bylaws of MGI, as applicable, (B) contravene or conflict with or constitute a violation of any provisions of any Applicable Law binding upon MGI, or (C) constitute a default in any material respect under or give rise to any right of termination, cancellation or acceleration of, any agreement or instrument to which MGI is a party, or to a loss of any material benefit to which MGI is entitled.

10.2.5 There is no action, suit, investigation or proceeding pending against, or lo the knowledge of MGI, threatened against or affecting, MGI before any court, arbitrator or any governmental authority,

including but not limited to Regulatory Authorities, that in any manner challenges or seeks to prevent, enjoin, alter or materially delay the Contemplated Transactions, and, to the knowledge of MGI, there is no reasonably valid basis for any such action, suit investigation or proceeding to be brought.

10.2.6 As of February 28, 2001, the authorized capital stock of MGI consists of 30,000,000 shares of common stock and 10,000,000 shares of preferred stock. As of February 28, 2001, (i) 16,538,545 shares of MGI's common stock are issued and outstanding, (ii) no shares of MGI's common stock are issued and held in the treasury of MGI and (iii) 4,075,749 shares of MGI's common stock are reserved for issuance upon exercise of options, warrants, convertible securities or any other right to acquire shares of common stock. There are no shares of preferred stock outstanding or reserved for issuance upon exercise or conversion of options. The common stock to be issued to HHC in accordance with the terms of this Agreement, if, any, will be, when so issued, duly authorized, validly issued and outstanding and fully paid and non-assessable. Such shares of common stock shall be freely tradable by HHC and shall not be subject to any preemptive rights.

10.2.7 MGI has heretofore delivered to HHC MGI's Form 10-K for the year ended December 31, 2000 ("10-K") and each and every report filed with the United States Securities and Exchange Commission ("SEC") since the date thereof. As of its date, except for any information corrected or superseded by subsequent filings with the SEC, such reports did not contain any untrue statement of material fact or omit to state a material fact required to be stated therein or necessary to make the statements therein, in light of

the circumstances under which they were made, not misleading. The audited consolidated financial statements of MGI and its subsidiaries, and the notes thereto included in the 10-K have been prepared in accordance with GAAP and present fairly the consolidated financial position of MGI and its subsidiaries as of the date thereof and the results of their consolidated operations and changes in consolidated financial position for the periods then ended. The unaudited consolidated financial statements included in MGI's 2000 quarterly reports filed on Form 10-Q ("10-Q") comply as to form in all material respects with the published rules and regulations of the SEC with respect thereto; and such unaudited financial statements are fairly presented in conformity with generally accepted accounting principles (except as permitted by Form 10-Q) applied on a basis substantially consistent with that of the audited financial statements included in the 10-K, subject to normal year-end adjustments. Except as and to the extent reflected or reserved against in the balance sheet included in the 10-K or 10-Qs, in the notes thereto or as covered by valid and collectible insurance or other collectible claim for reimbursement, except as set forth in a Schedule referred to in this Agreement or in a press release issued by MGI since the tiling of the most recent 10-Q, there has been no material adverse change in the business, properties or financial condition of MGI and its subsidiaries taken as a whole,

10.2.8 The persons executing this Agreement on behalf of MGI are duly authorized to do so and by so doing have bound MGI to the terms and conditions of this Agreement.

10.2.9 MGI understands and acknowledges that, as of the Effective Date hereof, there is no assurance

that there is or will be a market for the Products, and MGI expressly assumes the risk that the Products will be commercially marketable. HHC shall have no liability to MGI of any kind, nor shall MGI be entitled to a return or a refund of any portion of the payments specified at Article 7 hereof if, for any reason, the Registration is not granted in any part or the whole of the Territory or a commercial market does not develop for the Product.

10.2.10 MGI has been given full and complete access to such information and records of HHC as it deemed appropriate to conduct due diligence and such due diligence has been performed to the full satisfaction of MGI.

ARTICLE 11 - LIABILITIES, INDEMNITIES AND INSURANCE

11.1 MGI shall he fully liable for and shall defend, indemnify and hold HHC and its Affiliates, officers, directors and employees wholly free and harmless from and against any and all liabilities, damages, losses, costs, taxes, expenses (including reasonable attorneys' fees and other expenses of litigation and arbitration), claims, demands, suits, penalties, judgements or administrative and judicial orders arising out of or resulting from any claim, suit or proceeding to the extent arising out of or resulting from (a) the use of the Know-how, the Trademark and the Patent in the Territory by MGI (except to the extent provided in Article 11.2 below); (b) any failure by MGI, its local distributors or Affiliates to comply with any applicable laws, regulations and/or administrative decision regarding the Registration and/or the Products; (c) the performance by MGI of its obligations as HHC's FDA Agent and/or the management and performance by MGI of the post-Registration activities connected with

the NDA for the Products, as described at Article 4.5 above; (d) the performance by MGI or its agents of the development work relevant to the Products as described at Article 5.3 above; (e) any defect in the results of the development work carried out by or on behalf of MGI as provided at Article 5.3 above; (f) the storage, distribution, sampling, record-keeping, analysis, transfer or sale of the Products by MGI or its agents; (g) the promotion, advertising and marketing of the Products by MGI or its Affiliates; (h) misuse of the Know how received hereunder by MGI or its agents; (i) failure of any Products supplied hereunder to comply with the applicable approved specifications in the event that such non compliance (1) could have been detected by MGI carrying out visual inspection on the supplied Products with ordinary diligence or (2) results from any Products which has been altered, changed, packed or re-packed, processed or otherwise treated other than in strict accordance with HHC's instructions and specifications; or (j) any negligent or wrongful act or omission and/or any breach by MGI or by any of its local distributors and/or Affiliates of any of MGI's obligations, representations and/or warranties hereunder.

11.2 HHC shall be liable for and shall defend, indemnify and bold MGI and its Affiliates, officers, directors and employees free and harmless from and against any and all liabilities, damages, losses, costs, expenses (including reasonable attorneys' fees and other expenses of litigation and arbitration), claims, demands, suits, penalties, judgements or administrative and judicial orders, but in no event in excess of the sums already paid by MGI under Article 7 hereabove, arising out of or in any way resulting from any claim, suit or proceeding to the extent arising out of or resulting from (a) a claim that the use of the Know-

how and the Patent infringes any intellectual property right of any third party (but only to the extent HHC is covered by Syntex in this regard pursuant to the applicable provisions of the Syntex Agreement); (b) any failure by HHC or its Affiliates to comply with any applicable laws, regulations and/or administrative decision regarding the Registration and/or the Products; (c) the performance by HHC or its agents of any development activities relating to the Products, as described at Article 4.2 above; (d) any defect in the results of the development work carried out by or on behalf of HHC as provided at Article 4.2 above; (e) the storage, distribution, sampling, record-keeping, analysis, transfer or sale of the Products by laic or its agents; (f) the promotion, advertising and marketing of the Products by HHC or its Affiliates; (g) misuse of the Know-how by HHC or its Affiliates; or (h) any negligent or wrongful act or omission and/or breach by HHC or its Affiliates of any of its obligations and/or warranties hereunder.

11.3 Being understood that each of the Parties hereto shall take all reasonable steps to avoid or mitigate any loss, damage or liability which might give rise to a claim under this Agreement, a Party seeking indemnification pursuant to this Article 11 (an "Indemnified Party) shall give prompt and full written notice to the Party from whom such indemnification is sought (the "Indemnifying Party") of the assertion of any claim, or the commencement of any action, suit or proceeding in respect of which indemnity is or may be sought hereunder, provided however that no failure to give such notice or co-operation shall relieve the Indemnifying Party of any liability and/or obligation hereunder (except to the extent the Indemnifying Party has suffered actual prejudice thereby). The Indemnifying Party shall have the sole right to control

the defense and settlement thereof. The Indemnified Party will give the Indemnifying Party such information with respect thereto as the Indemnifying Party may reasonably request and will co-operate with the Indemnifying Party in the defense of said claim, suit or proceeding as the Indemnifying Party may reasonably request The Indemnified Party shall not, except at its own cost, voluntarily make any payment or incur any expense with respect to any claim, suit or proceeding without the prior written consent of the Indemnifying Party.

In addition, the Indemnifying Party shall be subrogated to the rights of the Indemnified Party against any third party, and such Indemnified Party hereby assigns to the Indemnifying Party all claims, causes of action and other rights which the Indemnified Party may then have against any third party, including Affiliates and, in the case of HHC, against any contract manufacturer of the Products, with respect to the claim, suit or proceeding which is the subject of the claim for indemnification hereunder. Conversely, and without in any way limiting the obligation of either Party to indemnify the other Party as herein provided, to the extent that either Party shall fail to perform its indemnification obligations under this Article 11, such Party owing a duty of indemnification hereby assigns to the other Party all claims, cause of action and other rights which the Party owing such duty may then have against any third party, including Affiliates and, in the case of HHC, against any contract manufacturer of the Products, with respect to the claim, suit or proceeding.

It is understood and agreed that the operation and application of this Article 11.3 are however subject to any right of Syntex (USA.) Inc. under articles 8.3, 8.4

and 8.5 of the Syntex Agreement, which are hereby acknowledged and accepted by MGI.

11.4 MGI shall be solely responsible towards its customers for handling all matters concerning the Products subject to cooperation with HHC on any recall or other regulatory matters that may be injurious to HHC. MGI shall be responsible for any expired Products, whether stored by MGI and/or its local distributors or returned by wholesalers, pharmacists, doctors, hospitals to whom said Products have been sold. MGI shall indemnify, defend and hold HHC and its Affiliates, directors, officers and employees wholly free and harmless from and against any and all liabilities, damages, losses, costs, expenses (including reasonable attorneys' fees and other expenses of litigation and arbitration), claims, demands, suits, penalties, judgements or administrative and judicial orders arising therefrom; except with respect to any recall or other regulatory action arising from any breach by HHC or its Affiliates of any warranty, representation or other material obligation contained in this Agreement or the negligence or willful misconduct of HHC or its Affiliates.

11.5 Each Party shall indemnify and hold the other Party wholly harmless from and against any and all liabilities, damages, losses, costs, expenses (including reasonable attorneys' fees and other expenses of litigation and arbitration), claims, demands, suits, penalties, judgements or administrative and judicial orders arising out of any behavior contrary or in excess to the provisions of Article 18.1 hereunder.

11.6 THE SOLE REPRESENTATIONS AND WARRANTIES THAT ABC MAKES WITH RESPECT TO THE MATTER CONTEMPLATED BY THIS AGREEMENT ARE EXPRESSLY SET FORTH IN

ARTICLE 10.1. WITHOUT LIMITING THE GENERALITY OF THE FOREGOING, HHC MAKES NO REPRESENTATION OR WARRANTY OF ANY KIND, EXPRESS OR IMPLIED, OF MARKETABILITY, CAPACITY OR FITNESS FOR A PARTICULAR PURPOSE WITH RESPECT TO THE KNOW-HOW, THE PATENTS AND/OR THE PRODUCTS. NO ORAL OR WRIT TEN REPRESENTATION BY OR ON BEHALF OF HHC SHALL BE INTERPRETED TO CONTAIN ANY SUCH WARRANTY. NEITHER MGI NOR ANY OF ITS EMPLOYEES OR REPRESENTATIVES IS AUTHORISED TO GIVE ANY WARRANTIES OR MAKE ANY REPRESENTATION ON BEHALF OF HHC.

11.7 THE SOLE REPRESENTATIONS AND WARRANTIES THAT MGI MAKES WITH RESPECT TO THE MATTER CONTEMPLATED BY THIS AGREEMENT ARE EXPRESSLY SET FORTH IN ARTICLE 10.2 AND MGI HEREBY DISCLAIMS ALL OTHER REPRESENTATIONS OR WARRANTIES OF ANY KIND, EXPRESS OR IMPLIED. NO ORAL OR WRITTEN REPRESENTATION BY OR ON BEHAIF OF MGI SHALL BE INTERPRETED TO CONTAIN ANY SUCH WARRANTY. NEITHER HHC NOR ANY OF ITS EMPLOYEES OR REPRESENTATIVES IS AUTHORISED TO GIVE ANY WARRANTIES OR MAKE ANY REPRESENTATION ON BEHALF OF MGI.

11.8 NOTWITHSTANDING ANY OTHER PROVISION OF THIS AGREEMENT, NEITHER OF THE PARTIES SHALL BE LIABLE TOWARDS THE OTHER FOR INDIRECT, SPECIAL, PUNITIVE, EXEMPLARY, INCIDENTAL OR CONSEQUENTIAL DAMAGES, INCLUDING WITHOUT LIMITATION LOSS OF PROFITS OR REVENUES,

REGARDLESS OF WHETHER SUCH DAMAGES WERE FORESEEABLE OR NOT. THIS CLAUSE WILL HOWEVER NOT BE APPLICABLE IN CASE OF BREACH BY MGI OF THE LIMITATIONS OF GRANTS AND THE NON-COMPETITION OBLIGATIONS STATED AT ARTICLE 2 AND BREACH BY EITHER PARTY OF THE CONFIDENTIALITY AND NON-USE OBLIGATIONS STATED AT ARTICLE 14 OF THIS AGREEMENT.

11.9 Each Party agrees to procure and maintain in full force and effect during the term of this Agreement valid and collectible insurance policies in connection with its activities as contemplated herein. In particular, MGI at its own cost shall cause HHC and their respective employees, officers, directors and contractors to be added as additional named insured throughout the term of this Agreement on all policies of general commercial liability insurance and product liability insurance covering MGI, which coverage shall, when MGI either initiates clinical trials on the Products or begins marketing or distributing the Products for commercial sale or for promotional purposes, have limits of liability which are commercially reasonable in the Territory but shall be not less than USD 30,000,000 (United States Dollars thirty million) per loss occurrence. Within 5 (five) days of the Effective Date and of each beginning of each policy period, MGI shall provide HHC with a certificate evidencing the coverage required hereby and the amount thereof. Such coverage shall be with a reputable insurance company having at least an A.M. Best "A" rating and shall have to be maintained for not less than 6 (six) years following expiration or termination of this Agreement for any reason or if such coverage is of the "claims made" type, for ten years

following expiration or termination of this Agreement for any reason.

ARTICLE 12 - THE PATENTS

12.1 MGI agrees that any Products distributed, promoted, marketed and sold by it will be marked with a notice of patent rights as necessary or desirable under applicable law to enable the Patent to be enforced to the maximum degree.

12.2 MGI shall cooperate with HHC as may be reasonably requested by HHC and at HHC's expense for the purpose of filing for and obtaining patent extensions and supplementary or complementary protection certificates, if available, of the Patents under the relevant applicable laws of each country of the Territory.

12.3 HHC hereby undertakes that it shall use commercially reasonable efforts to cause Syntex to comply with its obligations under the Syntex Agreement with regard to maintenance, defense and enforcement of the Patents in the Territory. In the event that Syntex fails to maintain, defend and enforce such Patents, then HHC shall use commercially reasonable efforts do so, to the fullest extern permissible under the relevant provisions of the Syntex Agreement.

12.4 MGI shall promptly inform HHC in writing upon its becoming aware of any possible third party infringement of the Patents. HHC shall thereafter promptly report the case to Syntex in accordance with the relevant provisions of the Syntex Agreement, for appropriate action by Syntex and/or HHC. MGI shall provide assistance, bearing exclusively its own costs, as may be reasonably requested by HHC.

12.5 MGI shall promptly inform HHC in writing upon its becoming aware of any notice or claim that the distribution, promotion, marketing and sale of the Product in the Territory for the Field in accordance with the terms and conditions of this Agreement infringe any third party's patent rights, or in the event of the commencement of any suit or action for infringement of any such third party's rights. HHC shall therefore promptly report the case to Syntex in accordance with the relevant provisions of the Syntex Agreement, for appropriate action. MGI shall not settle or compromise any such suit or action without the prior written consent of HHC and shall provide assistance, bearing exclusively its own internal costs, as may be reasonably requested by HHC.

12.6 MGI shall fully co-operate with HHC in connection with any action or proceeding relating to the validity of the Patent, including if required being joined as a necessary party to such action or proceeding at HHC's expense.

ARTICLE 13 - THE SYNTEX AGREEMENT

13.1 MGI acknowledges and understands that the rights granted to it by HHC in this Agreement derive from the Syntex Agreement and are subject to the terms thereof, a copy of which with economic terms redacted MGI has reviewed. The Parties hereby acknowledge and agree that in case of any discrepancy or conflict between this Agreement and the Syntex Agreement, this Agreement shall be construed in a manner consistent with the Syntex Agreement, except for those obligations of HHC towards Syntex which do not have a material impact on MGI's obligations hereunder.

13.2 During the term of this Agreement, HHC agrees to comply in all material respects with its obligations under the Syntex Agreement to the extent necessary to preserve its rights in the Territory thereunder, except to the extent that such compliance is dependent upon MGI.

13.3 During the term of this Agreement, MGI agrees to act in compliance with the Syntex Agreement to the extent required by the Syntex Agreement, including without limitation any confidentiality restrictions contained therein.

13.4 MGI acknowledges and agrees that HHC has acquired certain rights in and to the Compound pursuant to the Syntex Agreement and that any and all rights that MGI is acquiring pursuant to this Agreement arc subject to, in all cases, the Syntex Agreement. Further, MGI acknowledges that under certain circumstances, Syntex has the right to terminate certain of HHC's rights under the Syntex Agreement. HHC shall promptly provide MGI with a copy of any notice of termination it may receive from Syntex under the Syntex Agreement and the Parties shall thereafter discuss in good faith appropriate steps to cure such termination event.

ARTICLE 14 - CONFIDENTIALITY

14.1 MGI shall treat as strictly confidential, and shall use solely for the purpose of and in accordance with this Agreement, the Know-how, Improvements and/or any information and/or document received hereunder or in connection with the Contemplated Transaction not generally known to the trade, including but not limited to non-public information relating to the Patent as well as the results of the development work performed hereunder (all hereinafter referred to

as the "Confidential Information"). MGI shall not make such Confidential Information available to any third Party, including any of its Affiliates, except to competent government agencies to which it will be necessary to disclose such Information, and in this case (a) strictly to the extent requested by said agencies and (b) only upon exercise of its best efforts to cause said agencies to maintain confidentiality thereof.

14.2 Such Confidential Information shall only be made available to such employees of MGI who are directly and necessarily involved in the authorized use of Confidential Information and who are subject to a secrecy obligation by contract, to the extent strictly necessary to perform their duties and obligations hereunder.

14.3 Notwithstanding expiration or termination of this Agreement for any reason, these confidentiality and non-use obligations shall continue until the Confidential Information has become generally known to the public, provided however that nothing contained herein shall in any way restrict or impair the right of MGI to use, disclose or otherwise deal with Information which MGI can demonstrate to HHC by clearly convincing documentation:

14.3.1 is or hereafter becomes part of the public domain through no act or omission of MGI, its employees, Affiliates and/or local distributors, or

14.3.2 MGI was in lawful possession of prior to receipt of the Confidential Information from HHC, or

14.3.3 previously was, or at any time hereafter is, received in good faith by MGI from sources other than HHC and which did not originate, directly or indirectly, from Syntex, or

14.3.4 at the time of disclosure., was known by MGI or an Affiliate or local distributor, or after disclosure was independently developed by MGI, an Affiliate or local distributor without use of the Confidential Information.

14.4 Prior to the publication or presentation of any information or data arising from the activities described at Article 5.3 above, MGI shall submit to HHC a summary of the proposed publication or presentation prior to the submission thereof for publication or presentation. The purposes for such prior submission are: (i) to provide HHC with the opportunity to review and comment on the contents of the proposed publication or presentation, (ii) to identify any Confidential Information to be deleted from the proposed publication or presentation, and (iii) to agree in good faith on the contents and timing of such proposed publication or presentation.

14.5 HHC shall keep strictly confidential, in the same way mutatis mutandis as provided here above for MGI in respect of Confidential Information, any MGI Confidential Information (as defined herein) received from MGI hereunder, except as otherwise specifically provided in this Agreement. As used herein, the term "Confidential Information" shall mean all information disclosed by MGI to HHC, relating to the markets, customers, suppliers, patents or patent applications, inventions, know-how, data or information, products, research and development, procedures, designs, formulas, business plans, financial projections, employees, consultants or any other similar aspects MGI's present or future business, whether such information is disclosed in written, oral, electronic, graphic or other format.

ARTICLE 15 - FORCE MAJEURE

15.1 If the performance of this Agreement is prevented or restricted by government action, war, fire, explosion, flood, strike, lockout, embargo, act of God, or any other similar cause beyond the control of the defaulting Party, the Party so affected shall be released for the duration of the force majeure, or such other period agreed between the Panics as being reasonable in all circumstances, from its contractual obligations directly affected by the force majeure, provided that the Party concerned shall:

15.1.1 give prompt notice in writing to the other Party of the cause of force majeure;

15.1.2 use commercially reasonable efforts to avoid or remove such cause of non-performance;

15.1.3 continue the full performance of this Agreement as soon as such cause is removed.

15.2 The Parties shall take all reasonable steps to minimize the effects of force majeure on the performance of this Agreement and shall, if necessary, agree on appropriate measures to be taken. Should the force majeure continue for more than 6 (six) months, then the other Party shall have the right to terminate this Agreement forthwith.

15.3 Notwithstanding anything contained in this Article 15, obligations to pay money accruing prior to the force majeure event are never excused by force majeure.

ARTICLE 16 - TERM

16.1 This Agreement comes into force at the Effective Date hereof. Unless terminated earlier pursuant to the provisions hereof and subject to the validity of the Syntex Agreement, it shall remain in force for a

period of .10 (ten) years from the date of launching by MGI of the first of the Products and, unless either of the Parties gives notice of termination to the other Party in writing 6 (six) months before the termination of the initial or of any extension period, it shall be automatically renewed for periods of 3 (three) years.

ARTICLE 17 - TERMINATTON

17.1 Each of the Parties reserves the right to terminate this Agreement in case of any substantial or persistent breach of any of the terms and conditions of this Agreement by the other Party, including, without limitation, as provided at Articles 2.12 and 7.3.6 above. The defaulting Party shall be given in writing a 60 (sixty)-day period, except as otherwise specifically provided, to fulfil its obligations hereunder and, if after such period it is still in breach of the Agreement, the other Party shall have the right to terminate this Agreement by written notice to the defaulting Party. In addition, MGI hereby acknowledges and agrees that HHC shall be entitled to terminate this Agreement by written notice to MGI in case of termination of any agreement between MGI and any third party for the supply of Products to MGI as per Article 2.5 above due to a breach by MGI.

17.2 Either Party shall have the right to terminate this Agreement upon written notice to the other Party, if such Party shall become insolvent or shall make an assignment for the benefit of creditors or become involved in receivership, bankruptcy or other insolvency or debtor relief proceedings, or any similar proceedings, or in proceedings, voluntary or forced, whereby the Party involved is limited in the free and unrestrained exercise of its own judgement as to the carrying out of the terms of this Agreement. The Parties intend that upon HHC's termination of this

Agreement pursuant to this Article 17.2, all rights granted hereunder to MGI shall be terminated and revert to HHC. The Patties acknowledge and agree that all rights and licenses granted pursuant to this Agreement are, and shall otherwise be deemed to be, for purposes of Article 365(n) of the Bankruptcy Code, licenses of rights to "intellectual property" as defined under Section 101(52) of the Bankruptcy Code, and that MGI, as a licensee hereunder, shall retain and may fully exercise all of its rights and elections under the Bankruptcy Code.

17.3 In case the ownership or control (as this tents is defined at Article 1.2 here above) of MGI or of a legal entity directly or indirectly owning or controlling MGI changes (whether by merger, consolidation, reorganization, take over, change in the ownership of the share capital or otherwise), details of any such change in ownership or control shall he notified in writing by MGI to HHC as soon as possible and in any case no later than 5 (five) days of its occurrence. HHC shall then have the right to terminate this Agreement by giving MGI or the new entity owning or controlling MGI 30 (thirty) days advance notice in writing if (i) the entity owning or controlling MGI has in its portfolio a product competing with the Products (as defined at Article 2.4 here above) and/or (ii) MGI's commitments and investments on the Products in terms of promotion and marketing efforts, sales force activities, sales performance etc. arc not maintained by said new entity.

17.4 If MGI does not achieve the annual minimum of sales as referred in Articles 7.3.6 and 8.7 hereabove (e.g., eighty-five percent (85%) of MGI's Unit Sales base forecast) in any country(ies) of the Territory in a given year starting from the second year from launch,

the Parties shall meet not later than February 28th of the following year to (a) discuss the market for the Products, the competitive environment and MGI's sales and marketing activities, plans and resources for the Products and (b) agree on a remedial plan to be implemented by MGI in such country(ies). MGI shall thereafter have a period of one hundred twenty (120) days to implement such remedial plan and if it fails to do so, HHC will have the right to terminate this Agreement with respect to the country or countries in which MGI failed to implement such plan upon thirty (30) days written notice to MGI.

17.5 HHC shall have the right to terminate this Agreement by written notice to MGI if MGI fails to launch the Products as provided in Article 8 hereabove, or if MGI or any of its agents, employees, Affiliates or distributors breaches the confidentiality and/or non use obligations provided for in Article 14 hereabove. MGI shall have the right to terminate this Agreement by written notice to HHC if HHC or any of its agents, employees or Affiliates breaches the confidentiality and/or non use obligations provided for in Article 14.5 hereabove.

17.6 Without limiting the generality of the foregoing, termination or expiration of this Agreement for any reason shall not extinguish any existing claims either of the Parties may have for indemnification and shall not preclude either of the Parties from pursuing any claim for indemnification such Party otherwise may have to the extent that the circumstances giving rise to such claim arose prior to, on or after the date of termination or expiration

17.7 Upon expiration or termination of this Agreement for any reason. MGI shall:

17.7.1 subject to Article 17.7.4 hereunder, promptly cease any use and/or exploitation of the Registration;

17.7.2 subject to Article 17.7.4 hereunder, promptly cease any use of the Trademark and not hold itself out as a distributor of the Products;

17.7.3 subject to Article 17.7.4 hereunder, promptly terminate using the Know-how, the Improvements and the results of the development work carried out in accordance with Article 5.3 hereunder and return or deliver all such materials to HHC without retaining copies, notes, summaries or translations thereof;

17.7.4 promptly terminate distributing, promoting, marketing and selling the Products onto the market, provided that it shall have a three-month period to sell its existing stock of Products, subject to payment of royalties hereunder. Any stock remaining at the expiry of said three months period shall be destroyed by MGI at MGI's expenses, unless otherwise directed by HHC.

17.8 Unless otherwise set forth herein, the Parties' remedies under this Agreement are intended to be cumulative and not mutually exclusive.

ARTICLE 18 - MISCELLANEOUS

18.1 Independent contractor status

The status of HHC and MGI under the business arrangement established by this Agreement is that of independent contractors. MGI shall perform as an independent contractor in relation to both HHC and MGI's customers and, accordingly, MGI shall

purchase the Products from HHC or HHC's nominee and resell them to its customers in its own name and for its own account. With the sole exception of the provisions of Article 4.5 here above regarding Mars role as HHC's FDA Agent, MGI has no authority whatsoever to act as an agent or representative of HHC nor any authority or power to contract in the name of or create any liability against or otherwise bind HHC in any way for any purpose, nor shall HHC have such authority or power to so bind MGI.

18.2 Notices

All reports, notices and communications given or made pursuant to this Agreement by one Party to the other shall be validly given or made for all purposes, in the absence of acknowledgement of receipt, on the date of mailing if mailed by registered airmail or by international courier to the addressee Party at the following addresses, respectively:

HELSINN HEALTHCARE SA
P.O. BOX 357
6915 Pambio-Noranco
SWITZERLAND;
For the attention of the Legal Department

MGI PHARMA INC.
6300 West Old Shakopee Road
Suite 110
Bloomington, MN 55438-2318
USA
For the attention of Manager, Legal Affairs

with a copy to:

Dorsey & Whitney LLP
220 5. 6th Street
Minneapolis, MN 55402
Attention: Timothy S. Hearn

18.3 Binding Effect. Subject to the provisions of articles 2.1, 2.8 and 18.6 herein, this Agreement shall inure to the benefit of, and be binding upon, the respective successors of the Parties.

18.4 Waiver. The failure of a Party to insist upon strict performance of any of the terms and conditions of this Agreement by the other Party shall not constitute a waiver of any of the provisions hereof and no waiver by a Party of any of said terms and conditions shall be deemed to have been made unless expressed in writing and signed by such waiving Party.

18.5 Interpretation.

18.5.1 The language of this Agreement is English. No translation into any other language shall be taken into account in the interpretation of the Agreement itself.

18.1.2 The headings m this Agreement are inserted for convenience only and shall not affect its construction.

18.5.3 Where appropriate, the terms defined in Article 1 hereabove and denoting a singular number only shall include the plural and vice versa.

18.5.4 References to any law, regulation, statute or statutory provision includes a reference to the law, regulation, statute or statutory provision as from time to time amended, extended or re-enacted.

18.6 Assignment. This Agreement and the licenses and other rights conferred upon MGI under this Agreement are personal to MGI and cannot be transferred, sublicensed, assigned or otherwise disposed of (by operation of law or otherwise) by MGI without the prior, written authorization of HHC, which authorization shall not be unreasonably withheld; provided,

however, that MGI shall be entitled to assign this Agreement without such consent in connection with a merger, acquisition or sale of substantially all of its assets or to any of its Affiliates, in accordance however with the criteria established at Article 17.3 hereabove HHC shall have the right to assign or transfer, in whole or in part, this Agreement to any of its Affiliates.

18.7 Statements to the Public. Neither HHC nor MGI shall make or procure or permit the making of any announcement or statement to the public with respect to this Agreement, its subject matter or any ancillary matter without the prior consent of the other Party, which consent shall not be unreasonably withheld.

The wording and the timing of any press release or of any other announcement and/or statement to the public shall have to be agreed upon in advance between the Parties.

Nothing herein shalt prohibit MGI from disclosing information to the extent required by the U.S. Securities and Exchange Commission, Nasdaq or other similar authorities. It is however understood and agreed that (a) the contents of any copy of this Agreement, or of any other agreement between the Parties, which has to be sent to the SEC shall have to be previously agreed upon between the Parties and shall be in redacted form to maintain the confidentiality of proprietary and/or competitivity sensitive information, and (b) MGI shall use its best efforts to obtain authorization by the SEC to keep confidential any information which is deemed to be confidential by the Parties or any of them or which may, in either Party's opinion, put a competitive advantage to third parties.

18.8 Expenses. Unless specifically and expressly provided for to the contrary in this Agreement, each of the Parties shall bear its own expenses incurred in connection with the performance of this Agreement.

18.9 Survival. The following provisions shall survive expiration or termination of this Agreement for any reason: Articles I (whole clause), 3.4, 4.2 (last sentence), 4.7 (last sentence), 9.1, 11 (whole clause), 14 (whole clause), 17.6 through I7.8, 18 (whole clause), 20 (whole clause) and 21 (whole clause).

ARTICLE 19 - APPENDICES

19.1 The following Appendices shall he an integral part of this Agreement:

Appendix 1: List of Know-how Items

Appendix 2: Patents

Appendix 3: Products

Appendix 4: Development Chart

Appendix 5: Post-Registration Regulatory Activities

Appendix 6: Adverse Events Reporting

Appendix 7: Products Recall Procedure

Appendix 8: Escrow Agreement

Appendix 9: MGI's unit sales base forecast - Annual Minimum Sales

Appendix 10: Promotion and Marketing Activities

ARTICLE 20 - LAW TO GOVERN AND ARBITRATION

20.1 This Agreement shall be governed by and construed in accordance with the law of Switzerland.

20.2 It is the express decision of the Parties that any dispute which may arise between the Parties concerning this Agreement, which cannot be settled amicably, shall be submitted to arbitration for final decision. Also, any dispute as to the applicability of the arbitration clause shall he subject to arbitration.

Notwithstanding the above, each Party expressly reserves the right to seek judicial relief from a court of competent jurisdiction if the other Party is or appears to be in violation of such other Party's obligations of non-use and non-disclosure under Article 14 above, including, without limitation, any injunction or other preliminary relief.

20.3 It is expressly agreed that arbitration shall be held in English language in Geneva (Switzerland), and conducted under the Rules of Arbitration of the International Chamber of Commerce. The court of arbitration shall consist of three arbitrators. Each Party is entitled to nominate one arbitrator. If, within one month after receipt of the request for arbitration filed by one Party, the other has not yet appointed an arbitrator, such arbitrator shall be appointed by the International Court of Arbitration of the International Chamber of Commerce on request of the first Party, The two arbitrators shall nominate the president of the court of arbitration, who shall be a lawyer qualified to practice and currently practicing as an attorney-at-law or as a judge. If they cannot come to terms within one month, the president of the court of arbitration shall be nominated by the International Court of Arbitration of the International Chamber of Commerce, on request of the more diligent Party.

20.4 If one of the arbitrators is unable to fulfil his/her duties for any reason the Party having nominated him/her shall nominate another arbitrator

within one month, otherwise this arbitrator will be nominated by the International Court of Arbitration of the International Chamber of Commerce.

20.5 If the arbitrators or the president have to be replaced, the proceedings do riot have to he started anew and will continue at the point where they were stopped.

20.6 The court of arbitration is hereby expressly instructed to act with most diligence and to keep any term as short as possible and to render the decision as soon as possible.

20.7 The Parties hereby stipulate that any arbitration hereunder shall be subject to the following rules: (a) the arbitrators may not award or assess punitive damages against either Party; and (b) each Party shall bear its own costs and expenses of the arbitration and one-half (112) of the fees and costs of the arbitrators, subject to the power of the arbitrators, in their sole discretion, to award all such reasonable Costs, expenses and fees to the prevailing Party.

20.8 The Parties agree that the arbitrator's award shall be the sole and exclusive remedy between them regarding any claims, counter-claims, issues or accountings presented or pled to the arbitrator and that any costs, fees or taxes incident to enforcing the award shall be, to the maximum extent permitted by law, charged against the Party resisting such enforcement.

20.9 Notwithstanding the foregoing, any Party may bring a case of action against the other Party before any court of competent jurisdiction at the domicile of the defendant Party, if and to extent that any arbitral award rendered in the arbitration proceedings is unenforceable.

20.10 Subject to the provisions of Article 20.9, in the event that an award is rendered pursuant to this Article 20 by an arbitrator in favor of HHC, the Parties acknowledge and agree that such award shall be enforceable by HHC. and MGI hereby consents to the exclusive jurisdiction for purposes of enforcement of any such award against MGI to the United States District Court for the District of Delaware, or, if jurisdiction or venue cannot be laid therein, the jurisdiction of any courts in the Stale of Delaware. Each of the Parties hereby consents to the exclusive jurisdiction of such courts (and of the appropriate appellate courts) for the purposes set forth above.

ARTICLE 21 - ENTIRETY OF AGREEMENT AND SEVERABILITY

21.1 This Agreement supersedes all prior agreements and understandings, whether oral or written, made by either Party or between the Parties and constitutes the entire agreement of the Parties with regard to the subject matter hereof. This Agreement shall not be considered extended, cancelled or amended in any respect unless done so in writing and signed on behalf of the Parties hereto.

21.2 The Patties hereby expressly state that it is the intention of neither Party to violate any rule, law and regulations. If any provision of this Agreement is rendered invalid or unenforceable, the Parties agree to renegotiate such provision in good faith and to replace it with valid and enforceable provisions in such a way as to reflect as nearly as possible the intent and purpose of the original provision.

IN WITNESS WHEREOF, the Parties hereto have caused this Agreement to be executed in duplicate by their duly authorized officers.

For and on behalf of
HELSINKI HEALTHCARE SA

/s/ Ricardo Braglia
Ricardo Braglia
Managing Director

/s/ Enrico Braglia
Enrico Braglia
Managing Director

For and on behalf of
MGI PHARMA, INC.

/s/ Charles N. Blitzer
Charles N. Blitzer
President and Chief Executive Officer

/s/ Leon O. Moulder, Jr.
Leon O. Moulder, Jr.
Executive Vice President

LEGAL REVIEW AND APPROVAL

FIRST APPENDIX

To an Agreement between HEISINN HEALTHCARE SA and MGI PHARMA INC. dated April 6th 2001

LIST OF KNOW-HOW ITEMS

See enclosed documents

Chemistry, Manufacturing and Controls Know-how

The CMC Know-how on the Compound is included in the IND 39,797 and the relative correspondence with FDA up to February 28, 2001.

Pre-clinical Know-how

The Pre-clinical Know-how on the Compound is described in the following list and it includes all final reports available up to February 28, 2001.

Note: Studies coded "PALO - ## - ##" are sponsored by HHC.

Pre-clinical studies

Receptor Binding, Cardiovascular, Respiratory and Renal Activity

AT 6032
E.H.F. Wong
The receptor binding profile of RS-25259-197 at 5HT, and other receptors using radioligand binding techniques

AT 6036
K Leung
Activity of RS-25259-197 at 5-HT receptors in isolated tissues

AT 6373
E. Leung
Activity of RS-25259-197 at 5-HT, receptors in guinea pig ileum

AT 6976
E. Leung
Effect of RS-25259-197 at 5-HT, receptors, in vitro

CL 6721
D.W. Bonhaus and D.N. Lowy
Saturation, competition and kinetic analysis of [^{3}H]-RS-25259-197 binding

AT 6325
L. B. Jakeman
Distribution of [^{3}H] RS-25259-197 binding sites in rat and mouse brain by quantitative autoradiography

AT 5964
R. Alvarez
Effect of RS-25259-197 on 5-HT, receptors positively coupled to adenylate cyclase in guinea pig hippocampal membranes

AT 6446
L. A. Perkins
The effect of RS-25259-197 at 5-HT, receptors and on substance P in vitro

AT 5618
C.H. Lee
The effects of intravenous administration of RS-25259-197 on the bradycardic response to 2-methyl-5-hydroxytryptamine in anesthetized rats

AT 5763
C.H. Lee
The effects of intra-duodenal administration of RS-25259-197 on the bradycardic response to 2-methyl-5-hydroxytryptamine in anesthetized rats

AT 5389
C.H. Lee
The effects of topical application of RS 25259-197 on the bradycardic response to 2-methyl-5-hydroxytryptarnine in anesthetized rats

AT 5484
C.H. Lee
The effects of topical application of an aqueous solution of RS-25259-197 on the bradycardic response to 2-methyl-5-hydroxytryptaminc in anesthetized rats

AT 5491
C.H. Lee
The effects of topical application of RS-25259-197 on the bradycardic response to 2-methyl-5-hydroxytryptarnine in anesthetized cats

AT 5493
L.D. Wood and L.G. Johnson
Hemodynamic effects of 1S-25259-197 and ondansetron administered intravenously to anaesthetized dogs

AT 6242
C.Calder
The effect of RS-25259-197 on intra-atrial, intraventricular and atrioventricular conduction in the anaesthetized dog

PALO-99-48
A.I. El Amrani
Palonosetron, RS-17825-007 and RS-42358-197: evaluation of effect on cardiac action potential in isolated canine Purkinje fibres

PALO-99-49
E.Martel
Palonosetron evaluation of effects on blood pressure, heart rate and electrocardiogram after single intravenous dosing in conscious dogs of both sexes

PALO-00-10
K.Lansdell
Effect of Palonosetron on HERG currents recorded from stably transfected HEK 293 cells

AT 6168
L.G. Johnson
Interaction of RS-25259-197 with autonomic agents in anesthetized dogs

AT 6161
D. Martin and P. Hicks
Effect of RS-25259-197 on respiratory function and blood pressure in anesthetized dogs

AT 6005
K.D. Lake
The effect of RS-25259-197 on renal function in conscious, saline-loaded rats

Principal Activity and Pharmacology Auxiliary Studies

AT 6929
M.L. Turke
Effect of intravenously administered RS-25259-197 and ondansetron on cisplatin-induced emesis in dogs

AT 6030
M.L. Turke
Effect of RS-25259-197 and ondansetron on ducarbazine-indueed emesis in dogs

AT 6002
M.L. Turke
Effect of RS-25259-197 and ondansetron on mechlorethamine-induced emesis in dogs

AT 6001
M.L. Turke
Effect of RS-25259-197 and ondansetron on actinomycin D-induced emesis in dogs

AT 6003
M.L. Turke
Duration of action of intravenously administered RS-25259-197 and ondansetron on cisplatin-induced emesis in dogs

AT 6033
J.I. Gianettoni
Duration of action of intravenously administered RS-25259-197 on cisplatin-induced emesis in dogs

AT 6027
M.L. Turke
Therapeutic effect of intravenously administered RS-25259-197 and ondansetron on cisplatin-induced emesis in dogs

AT 6028
M.L. Turke
Effect of orally administered RS-25259-197 and ondansetron on cisplatin-induced emesis in dogs

AT 6313
J.I. Gianettoni
Correlation of anti-emetic activity and plasma levels of RS-25259-197 in cancer chemotherapy treated dogs

AT 5531
M.L. Turke
Effect of RS-25259-197 and ondansetron on cyclophosphamide-induced emesis in dogs

AT 6004
J.I. Gianettoni
Effect of RS-25259-197, ondansetron and granisetron on protoveratrine A-induced emesis in dogs
Comment: study invalidated

AT 6035
J.I. Gianettoni
Effect of RS-25259-197, ondansetron, and granisetron on copper sulfate-induced emesis in dogs

AT 6034
J.I. Gianettoni
Effect of RS-25259-197, ondansetron, and granisetron on apomorphine-induced emesis in dogs

AT 6664
M. R. Perry
Effect of intravenously administered M-25259-197 on cisplatin-induced emesis in ferrets

AT 5999
M.R. Perry
Effect of orally administered RS-25259-197 on cisplatin-induced emesis in ferrets

AT 6031
M.R.Perry
Duration of effect of orally administered RS-25259-197 on cisplatin-induced emesis in ferrets

AT 5244
M.L. Turke
Effect of RS-25259-197 on gastric emptying of a test meal in rats

AT 5985
J.L. Nunes
The effect of RS-25259-197 on the gross behavior of mice

AT 5452
C. Ward
The effects of RS-25259-197 on feeding behavior

AT 6037
E. Wong
An assessment of the actions of RS-25259-197 on mouse behavior in the black: white test box

PALO-99-11
C.N. Williams
Palonosetron hydrochloride: assessment of proconvulsant activity in mice following oral administration

AT 6777
W. R. Waud and J.D. Prejean
In vivo combination chemotherapy evaluation of RS-25259 HCI and cisplatin against murine P388 Leukemia

ADME

AT 6303
P. Weller et al.
Pharmacokinetics of RS-25259-007 after single oral doses of RS-25259-197 administered to male rats

AT 6304
P. Weller et al.
Pharmacokinetics of RS-25259-007 after single oral doses of RS-25259-197 administered to dogs

AT 6302
P. Weller et al.
Pharmacokinetics of RS-25259-007 and its N-oxide metabolite following once daily oral doses of RS-25259-197 administered to male rats over five days

AT 6301
P. Weller et al.
Plasma pharmacokinetics of RS-25259-007 and its N-oxide metabolite following once daily oral doses of RS-25259-197 administered to female dogs over five days

AT 5975
P. Weller et al.
Metabolic disposition and tissue distribution of [14C]-RS-25259-l97 after a single intravenous dose to rats

AT 6264
P. Weller et al.
Metabolic disposition following single intravenous and oral doses of [14C]-RS25259.197 and tissue

distribution after a single intravenous dose of [14C]-RS-25259197 to rats

AT 6285
P. Weller and M. Young
Metabolic disposition and tissue distribution to brain, eye and intestines after a single intravenous dose of [14C]-RS-25259-197 to pigmented rats

AT 5976
P. Weller et al.
Metabolic disposition of [14C]-RS-25259-197 after single intravenous and oral doses to dogs

DM 1078
P. Weller et al.
Metabolic disposition of [14C]-RS-25259-197 after single intravenous and oral doses administered to Cynomolgus monkeys
Comment: Draft report available (no further finalization performed by Syntex)

CL 6204
L. Brown and O. Weller
Binding of RS-25259-197 to plasma protein in vitro

PALO-00-02

Identification of M4

Step 1:

S. Madden

Investigation of [14C]-Palonosetron Metabolism in Human Hepatic Microsomes

Step 2:

G. McCorquodale

Investigation to Assess for the Presence and Structural Equivalence of Metabolic M4 in human

Urine Versus That formed by Incubation of [14C]-Palonosetron with Human Hepatic Microsomes

Toxicology Studies

Acute Toxicology

AT 5921
A. J. Sonderfan
Acute intravenous toxicity study in mice with RS-25259-197

AT 5939
A. J. Sonderfan
Acute intravenous toxicity study in rats with RS-25259-197

AT 5922
A. J. Souderton
Acute intravenous toxicity study in dogs with RS-25259-197

AT 6284
F.D. Andrew
Acute oral toxicity study in rats with R5-25259-197

AT 6268
F.D. Andrew
Acute oral toxicity study in Beagle dogs with RS-25259-197

Repeated-dose Toxicology

AT 5962
A. J. Sonderfan
Intravenous 1-month toxicity study in rats with RS-25259-197

PALO-99-19
C. Green
Palonosetron hydrochloride: intravenous administration tolerance study in the dog

AT 5963
A. J. Sonderfan
Intravenous 1-month toxicity study in dogs with RS-2.5259-197

AT 6329
F.D. Andrew
One-month oral toxicity study in rats with RS-25259-197

AT 6328
F.D. Andrew
One-month oral toxicity study in Beagle dogs with RS-25259-197

Subchronic Toxicology

AT 6665
A.J. Sonderfan
Oral three-month toxicity study with RS-25259-007 in rats

AT 6751
A.J. Sonderfan
Three-month oral dose-ranging study of RS-25259-197 in mice

AT 6787
A.J. Sonderfan
Oral three-month toxicity study with RS-25259-007 in dogs

Chronic Toxicology

PALO-99-08
T. Smith
Palonosetron hydrochloride: 26 week intravenous administration toxicity study in the rat with a 4 week treatment-free period

PALO-99-08
T.Smith
Palonosetron hydrochloride: 9 months intravenous administration toxicity study

Carcinogenicity

AT 7455
P. Penumarthy
Oral gavage carcinogenicity study in rats with Palonosetron (RS-25259-197) – Study termination report
Comment: Final report abbreviated

AT 7464
P. Penumarthy
Oral gavage carcinogenicity study in mice with Palonosetron (RS-25259-197) – Study termination report
Comment: Final report abbreviated

Reproductive Toxicology

AT 6700
A.J. Sonderfan
Oral male fertility and reproduction study of RS-25259-007 in rats

AT 6267
F.D. Andrew
Intravenous male fertility study with RS-25259-197 in rats

AT 6750
A.J. Sonderfan
Oral female fertility and early embryonic development study of RS-25259-197 in rats

AT 6756
A.J. Sonderfan
Oral teratology study with RS-25259-197 in rats

AT 6755
A.J. Sonderfan
Oral teratology study with RS-25259-197 in rabbits

PALO-99-13
J. Ridings
Palonosetron hydrochloride: oral (gavage) study or pre- and postnatal development in the rat

Mutagenicity

AM 0400
R.H.C. San and S.J.Elson
Salmonella/Mammalian-microsome pre-incubation mutagenicity assay (Ames test) and Escherichia coli WP2 uvrA reverse mutation preincubation assay

AM 0402
C.A.H. Bigge and C.I. Sigler
CHO/HGPRT mutation assay

AM 0401
D.L. Putman and M.J. Morris
Chromosome aberrations in Chinese Hamster Ovary (CHO) cells

AM 0399
H. Murli
Mutagenicity test on RS-25259497 in vivo micronucleus assay

PALO-99-38
L. Golzio
Palonosetron: unscheduled DNA synthesis in rat liver cells in vivo

Juveniles Toxicology

PALO-99-25
J.E. Ridings
Palonosetron hydrochloride: range-finding toxicity study in juvenile rats by the subcutaneous mute

PALO-99-12
J.E. Ridings
Palonosetron hydrochloride: 28-day subcutaneous toxicity study in juvenile rats

PALO-99-41
J.E. Ridings
Palonesetron hydrochloride: range-finding toxicity study in juvenile dogs by the intravenous route

PALO-99-22
J.E. Ridings
Palonosetron hydrochloride: 28-day intravenous toxicity study in the juvenile dog

Special Toxicology Studies

AT 5923
A.J. Sonderfan
Vein irritation study in the rabbit with an intravenous formulation of RS-25259-197

PALO-99-30
W.D. Ruddock
Palonosetron: local intravenous tolerance study in the rabbit

AT 6276
F.D. Andrew et al.
Dermal irritation study in rabbits with transdermal formulations containing RS-25259-007

AT 6279
F.D. Andrew

Dermal sensitization study in guinea pigs with transdermal formulation containing RS-25259-007

CL 5911
A.J. Sonderfan
In vitro eompatibility testing of RS-25259-197 using human blood

PALO-99-28
B.V. Bailey and H. Renton
Validation of an analytical procedure for the determination of palonosetron and its metabolite RS-17825-007 in dog plasma (lithium heparin) using protein precipitation and liquid chromatography with tandem mass spectrometric detection

PALO-99-29
B.V. Bailey and K. Triffitt
Validation of an analytical procedure for the determination of palonosetron and its metabolite RS-17825-007 in mouse plasma (lithium heparin) using protein precipitation and liquid chromatography with tandem mass spectrometric detection

PALO-99-30
W.D. Ruddock
Palonosetron: local intravenous tolerance study in the rabbit

Toxicology summary

AT 6824
Non clinical toxicology summary of RS-25259

Comment: summary of studies AT 5921, AT 5939, AT 5922, AT 6284, AT 6268, AT 5962, AT 5963, AT 6329, AT 6328, AT 6665, AT 6751, AT 6787, AT 6700, AT 6267, AT 6750, AT 6756, AT 6755, AM 0400, AM 0402, AM 0401, AM 0399, AT 5923, AT 6276, AT 6279, CL 5911.

Clinical Know-how

The Clinical Know-how on the Compound is described in the following list and it includes all final reports available up to February 28, 2001.

Clinical Studies

Phase 1 Studies (Clinical Pharmacology)

Study 2092
(RS-25259-197
RGR/25259S2092/USA)

R. Stoltz
A single dose ascending dose safety and pharmacokinetics study of IV RS-25259 in healthy volunteers

Study 0100
(RS-25259-197
2525950100)
M. Tei
A single-dose safety and pharmacokinetics study of RS-25259 (IV bolus dose) in healthy volunteers

Study 0101
(RS-25259-197
2525950101)
M. Tei
A single-dose safety and pharmacokinetics study of RS-25259 (oral solution) in healthy volunteers

Study 2236
(RS-25259-007
RGR/25259S2236/USA)
R. Stoltz
Single ascending-dose safety and pharmacokinetics study of an oral solution of RS-25259-007 in healthy volunteers

Study 2216
(RS-25259-197
(RGR-259,2216/USA)
R. Stoltz
Plasma pharmacokinetics, metabolism, and excretion of [14C]-RS-25259-197 after intravenous injection

Study DM992
(RS-25259-197
Report number: DM992)
P. Weller
Dosimetry estimates for the intravenous administration of a single 56 uCi/70kg (10ug/kg) dose of [14C]-RS-25259-197 to human volunteers

Phase 2 Studies

Study 2330
(RS-25259-197
25259S2330)
S. Solish et al.
A dose-ranging efficacy, safety, and pharmacokinetic study of single intravenous doses of RS-25259 for prevention of nausea and vomiting in chemotherapy-naive cancer patients receiving highly emetogenic chemotherapy

Study 2332
(RS-25259-197
25259S2332)
S. Solish et al.
A dose-ranging efficacy, safety, and pharmacokinetic study of single oral doses of RS-25259 for prevention of nausea and vomiting in chemotherapy-naive cancer patients receiving highly emetogenic chemotherapy

Study 2500
(RS-25259-197
25259S2500)
D. McHugh et al.
A dose-ranging safety and efficacy comparison of four dose levels of intravenous RS-25259 to placebo in the prevention of postoperative nausea and vomiting following abdominal and vaginal hysterectomy

Study 2502
(RS-25259-197
25259S2502)
D. McHugh dal.
A dose-ranging safety and efficacy comparison of four dose levels of oral RS-25259 to placebo in the prevention of postoperative nausea and vomiting following laparoscopic procedures

Study 2120
(RS-25259-197
RGR/25259S2120/USA)
Rodriguez G.
A safety, antiemetic, and efficacy and pharmacokinetic study of single-dose IV RS-23259-197 in cisplatin-naive cancer patients receiving high-dose cisplatin chemotherapy

Regulatory Know-how

The Regulatory Know-how on the Compound is described in the following list and it includes all the correspondence with FDA from the submission of the IND 39,797, until February 28, 2001.

Note: Syntex correspondence from June 2nd 1992 to July 23rd 1998 is available only as hard copy and not as electronic file.

Date	*Document*	*Summary*
July 31,1998	Amendment #54	Transfer of Ownership from Syntex (USA.) inc. to Heisinn SA
August 3, 1998	Amendment #55	Transfer of Syntex IND 39,797 (RS-25259-197, Palonosetron) to Heisinn Heathcare SA
September 29, 1998	Telephone to Kati Johnson	IND 39,797 program input; end of phase 2 meeting information. IND 42,886 program status
November 5, 1998	Telephone to Dr. Jasti Choudary	Request for pre-meeting.
November 12, 1998	Amendment #56	Preclinical program backgronnd package. Study termination reports-Syntex carcinogenicity studies. Cross-reference to IND 42,886 Palonostron hydrochloride Oral
November 13, 1998	Telephone to Kati Johnson	Follow-up on pre-clinical submission (Amendment #56). Clinical meeting

		request End of phase 2 meeting guidance
December 1, 1998	Telephone to Kati Johnson	Follow-up on pre-clinical submission (Amendment #56). Clinical program discussion. End of phase 2 meeting planning
December 9, 1998	Telephone to Kati Johnson	Follow-up on pre-clinical submission (Amendment #56). End of Phase 2 meeting discussion
December 23, 1998	Amendment #57	Request for End of Phase 2 meeting
December 23/24, 1998	Telephone from Melody McNeil, and Doris	End of Phase 2 meeting request letter
December 28, 1998	Telephone to Melody McNeil	Requirement for hard copy submission of End of Phase 2 meeting request letter
December 30, 1998	Telephone to Melody McNeil	End of phase 2 meeting request letter sent to FDA by Federal Express
January 6, 1999	Telephone from Kati Johnson	End of phase 2 meeting scheduling

January 11, 1999	Telephone from Kati Johnson	EOP2 meeting scheduled for March 15, 1999
January 19, 1999	Fax from FDA	EOP2 meeting scheduled for March 15, 1999
January 25/26/27, 1999	Telephone to Kati Johnson	Oral route of administration in dog. Preclinical contents in background document. Feedback on Company questions for EOP2 meeting
January 27, 1999	Amendment #53	Preclinical program background package; information to Amendment #56
February 1, 1999	Letter from FDA	Request for further information to complete change of sponsorship (Amendments #54 and #55).
February 4, 1999	Telephone from Michelle Kidwell	EOP2 meeting date change to Match 10, 1999
February 5, 1999	Fax from FDA	EOP2 meeting scheduled for March 10
February 3, 1999	Telephone from Kati Johnson	Rationale for oral route in the dog toxicology study
February 15, 1999	Amendment #59	Background Document for March 10,

		1999 End of Phase 2 meeting
February 19, 1999	Telephone to Dorothy	Receipt of Background Document (assistant to Kati Johnson)
February 24, 1999	Telephone to Dorothy	EOP2 meeting location
February 24, 1999	Telephone to Kati Johnson	Feedback on background document
February 24, 1999	Telephone to Kati Johnson	Regulatory Agent (additional conversation to Feedback on Background document telephone contact).
March 2, 1999	Telephone from Melody McNeil	Studies 2500 and 2502 efficacy results
March 4, 1999	Telephone to Melody McNeil	EOP2 FDA pre-meeting discussion feedback
March 4, 1999	Fax to FDA	Desk copy of studies 2500 and 2502
March 8, 1999	Telephone to Dr. Goldkind	Reviewer comments
March 8/10, 1999	Telephone from/to Kati Johnson	Follow-up on meeting with Goldkind End of phase 2 meeting planning
March 29, 1999	Amendment #60	Reply to FDA letter of February 1, 1999

		about the change of Sponsorship
March 31, 1999	Telephone to Melody McNeil	EOP2- scheduling of Biopharm meeting Request for meeting minutes
April 6/8, 1999	Telephone to/from Melody McNeil	Scheduling of biophamnaceutics part of end of phase 2 meeting. Request for overheads
April 9, 1999	Letter from FDA	Minutes of the meeting with FDA on March 19, 1999 (EOP2)
April 27, 1999	Telephone to Melody McNeil	Feedback of End of phase 2 meeting. Request for special protocol assessment.
April 29, 1999	Letter from FDA	FDA comments and recommendations referred to amendments #56 and #58 and the EOP2
April 29, 1999	Amendment #61	Palonosetron Hydrochloride IV End of Phase 2 Meeting Biopharmaceutics Teleconference Meeting Document
May 7, 1999	Amendment #62	Palonosetron Hydrochloride IV Revised study termination

		report-Syntex carcinogenicity study in mice. Cross-reference to IND 44886 Palonosetron Hydrochloride Oral
May 21, 1999	Letter from FDA	EOP2 biopharmaceutics conference call meeting minutes
June 4, 1999	Telephone from Michelle Kidwell	EOP2 biopharmaceutics conference call meeting minutes
June 4, 1999	Fax from FDA	EOP2-Biopharrn teleconference meeting minutes
June 7, 1999	Amendment #63	Palonosetron Hydrochloride IV Overheads presented in End of Phase 2 meeting
August 19, 1999	Amendment #64	Palonosetron Hydrochloride IV Phase 3 and Commercial Formulation
September 24, 1999	Amendment #65	1999 Annual Report
October 15, 1999	Amendment #66	PALO 99-08, CIE 1063/1 "Palonosteron Hydrochloride: 26 Weck Intravenous Administration Toxicity Study in the

		Rat with a 4 Week intravenous-free Period" IND Safety Report: Initial Written report.
November 11, 1999	Amendment #67	Authorized representatives for IND 39,797
November 24, 1999	Amendment #68	Phase 3 efficacy protocol PALO 99-03. Request for Special Protocol Assessment and Agreement
November 24, 1999	Amendment #69	Phase 3 efficacy protocol PAW 99-04. Request for Special Protocol Assessment and Agreement
November 30, 1999	Amendment #70	Toxicology study PALO-99-08; CLE-1063/1 "Palo nosteron Hydrochloride: 26 Week intravenous Administration Toxicity Study in the Rat with a 4 Week intravenous-free Period" Information Amendment: Follow-up and Additional Information to IND Safety Report, IND Amendment #66

December 10, 1999	Amendment #71	Phase 3 efficacy protocol PALO 99-05. Request for Special Protocol Assessment and Agreement
December 22, 1999	Amendment #72 (Protocol Amendment)	New protocol, PALO 99-39 Phase I ADME study
January 10, 2000	Letter from FDA	Reply to questions on Protocol PALO-99-04 (amendment #69 dated November 24, 1999)
January 10, 2000	Letter from FDA	Reply to questions on Protocol PALO-99-03 (amendment #68 dated November 24, 1999)
January 27, 2000	Letter from FDA	Reply to questions on Protocol PALO-99-05 (amendment #71 dated December 10, 1999)
February 17, 2000	Amendment #73 (Information Amendment)	Notification of change of address and phone number for Dr. Craig Lehmann at August Consulting, Authorized Representative for the IND

April 7, 2000	Amendment #74 (Protocol Amendment)	New Protocols, Phase 3 Protocols PALO-99-03, PALO-99-04, PALO-99-05
April 11, 2000	Telephone from Melodi McNeil	FDA review time for proposed pediatric protocols for purposes of obtaining 6 months claimed exclusivity
April 24, 2000	Amendment #75	Proposed Pediatric Study Request (PPSR)
April 26, 2000	Amendment #76	Phase 3 efficacy protocol PALO 00-01. Request for Special Protocol Assessment and Agreement
May 22, 2000	Amendment #77 (Protocol Amendment)	New protocol, Phase 3 Protocol PALO-99-06.
June 5, 2000	Amendment #78	Request for teleconference with Pharm/Tox Reviewer to Discuss Segment 3 Reprotox Study
June 5, 2000	Telephone to Ms. Melodi McNeil	1. Receipt of ReproTox Teleconference 2. Phone And Fax numbers for IND Safety Reports

June 9, 2000	Letter from FDA	FDA response to the PALO-00-01 FDAMA special protocol review request
June 12, 2000	Telephone to Ms. Melodi McNeil	Dr. Choudary's pharm/ tox review of IND Amendement #78, request for teleconference to discuss segment 3 reprotox study
June 14, 2090	Letter from FDA	Reply to June 5 and 6, 2000 correspondence requesting a meeting to discuss the acceptability of a completed Segment 3 pre- and post-natal study of palonosetron in rats
June 19, 2000	Amendment #79 (Protocol Amendment)	New Investigators, Phase 3 protocols PALO-99-03, PALO-99-04, PALO-99-05, PALO-99-06
June 30, 2000	Amendment #80	IND Safety Report-In-Vitro Purkinje Fiber Dog Data
July 10, 2000	Telephone from Melodi McNeil	Dr Talarico's letter dated 9 June 2000, Item #5. Published

		Historical I'lacebo Control
July 11, 2000	Telephone from Melodi McNeil	(1) Expected FDA letter re PALO Segment 3 Reprotox Study (reply to IND #78, 5 June 2000) (2) FDA letter of 9 June 2000 clarification of number of historical placebo patients in the literature
July 11, 2000	Telephone from Melodi McNeil	(1) FDA reply letter to Reprotox teleconference request (2) Historical Placebo controls studies
July 19, 2000	Amendment #81 (Protocol Amendment)	New Investigators, Phase 3 Protocols PALO-99-03, PALO-99-04, PALO-99-05, PALO.99-06
August 4, 2000	Amendment #82	Follow up to IND Safety Report – In Vitro Purkinje Fiber Dog Data (IND Amendment #80, submitted June 30, 2000)
August 9, 2000	Letter from FDA	FDA reply to amend-ment dated June 30, 2000 (serial #80)

August 14, 2000	Amendment #83 (Protocol Amendment)	New protocol, Pediatric Protocol PALO-99-07
August 17, 2000	Telephone to Melodi McNeil	Dr. Talarico's letter (received today) dated August 9, 2000, regarding our original plans to exclude patients from phase 3 trials who are taking comeds which prolong QTc
August 18, 2000	Amendment #84 (Protocol Amendment)	New investigators, Phase 3 Protocols PALO-99-04, PALO-99-05, PALO-99-06
August 18, 2000	Letter from FDA	Incorrect Zip Code in the letter dated August 9, 2000
August 24, 2000	Amendment #85 (Information Amendment)	Chronic Toxicology Draft Reports for Palonosetron, 9-month in Dug, 26-week in at
August 24, 2000	Amendment #86 (Protocol Amendment)	New Protocols, Phase 1 protocols PALO-99-35 and PALO-99-51
August 24, 2000	Telephone to Melodi McNeil	Serial 482 Follow-up to Safety Report (Serial #80), plan to allow comeds which

		prolong QTc in Phase 3 Trials
August 29, 2000	Amendment #87 (Information Amendment)	Phase 1 protocols PALO-99-35 and PALO-99-51
September 8, 2000	Amendment #88 (Information Amendment)	ReproTox Final Reports for Palonosetron
September 8, 2000	Amendment #89 (Information on Amendment)	Chemistry, Manufacturing, and Controls • Revised Drug Substance Specifications • New Stability Indicating Methods for Drug Substance and Drug Product • 12-Month Stability for Phase 3 Clinical Batches
September 20, 2000	Amendment #90 (Protocol Amendments)	• New Investigators, Phase 3 Protocols PALO-99-03, PALO-99-04, PALO-99-05, and PALO-99-06. • Change in Protocols, Protocol Amendment No. 2 for PALO-99-03,

		PALO-99-04, PALO-99-05, and PALO-99-06.
September 22, 2000	Telephone to Melodi McNeil	FDA feedback regarding the pediatric protocol is expected in one week
September 26, 2000	Amendment #91 (Protocol Amendment)	New Investigators, Phase 3 Protocols PALO-99-03, PALO-99-05, PALO-99-06, and PALO-99-07
September 26,2000	Letter from FDA	FDA reply to Pediatric Study Request PALO-99-07
September 28, 2000	Amendment #92	2000 IND Annual Report
October 16, 2000	Amendment #93 (Information Amendment)	Rat Carcinogenicity Study PALO-98-03, Decreasing Number of Survivors in High Dose Female Group – Request for Goidance. Cross-reference to IND 42,886, Palonosetron Hydrochloride Oral
October 17. 2000	Telephone to Melodi McNeil	Dr. Choudary's preliminary feedback regarding the loss rate in the high dose female group in the Palonosetron Rat

		Carcinogenicity Study
November 3, 2000	Telephone to Ms. Alcock Patricia	NDA Field Copy to Responsible FDA District Office
November 6, 2000	Fax to Melodi McNeil (2)	Serial #93, October 16, 2000 – Request for confirmation of Dr. Chondary's feedback of October 17, 2000 regarding the loss rate in the high dose female group in the Palonosetron Rat Carcinogenicity Study
November 9, 2000	Telephone to Melodi McNeil	Request for confirmation from Dr. Choudary/FDA regarding his earlier feedback (FDA Communication Report, 17 October 2000) to address loss rates in the high dose female group of the Palonosetron rat carcinogenicity study
November 14, 2000	Letter from Dr. Talarico	FDA letter from Dr. Talarico (undated and unsigned) postmarked 9 Nov 2000 - FDA evaluation of

		juvenile rat and dog tox studies, follow-up FDA requests, and FDA request for full reports and data for dog and in-vivo CVS studies
November 17, 2000	Amendment #94 (Protocol Amendment)	New Investigators, Phase 3 Protocols PALO-99-03, PALO-99-04, PALO-99-05, and PALO-99-06
November 22, 2000	Amendment #95 (Request for teleconference)	Request for teleconference to discuss the proposed NDA CMC strategy
November 22, 2000	Telephone to Melodi McNeil	Request for tele-conference to discuss the proposed CMC NDA strategy
November 24, 2000	Telephone from Melodi McNeil	Proposed teleconfer-ence to discuss the Palonosetron CMC strategy
November 30, 2000	Amendment #96 (Request for teleconference)	Request for Teleconference to Discuss the Proposed Pediatric Protocol PALO-99-07
December 01, 2000	Telephone to Melodi McNeil	Arrangements for pediatric protocol teleconference (serial #96) and the CMC

		strategy teleconfcrence (serial #95)
December 07, 2000	Telephone to Heleo Wilson	Proposed dates/times for CMC strategy teleconference requested in Serial #95, submitted 22 Nov. 2000
December 12, 2000	Telephone to Robert DeLap	Status of ICH Common Technical Document (CM) Implementation at FDA for NDAs
December 12, 2000	Telephone to Helen Wilson	Arrangement of date/ time for requested Palonosetron CMC teleconference
December 12, 2000	Amendment #97 (Response to FDA request for information)	Reply to FDA Letter Postmarked November 9, 2000, Regarding the 28-Day Juvenile Rat and Dog Studies and the in vivo Dog Cardiovascular Safety Study
December 13, 2000	Telephone to Helen Wilson	CMC strategy FDA Teleconference – 31 Jan date no longer available per FDA. FDA suggests Jan 31th or Feb 2nd

December 14, 2000	Telephone to Helen Wilson	Arrangements for Palonosetron CMC Strategy Teleconference
December 15, 2000	Telephone to Helen Wilson	FDA proposed dates/ times to convene FDA pediatric PALO-99-07 protocol teleconference
December 15, 2000	Fax from FDA	FDA fax confirmation of date/time and planned FDA attendees for the CMC Strategy teleconference of Jan 30, 2001,9-10:30 AM, and FDA request for Word 97 diskette with list of Sponsor's attendees and specific questions
December 18, 2000	Telephone to Melodi McNeil	1) Date/time to convene the FDA pediatric PALO-99-07 protocol teleconference. 2) Subsequent planned teleconferences to discuss FDA's replies to Special Protocol Assessments (PALO-99-03, PALO-99.04,

		PALO-99-05, and PALO-00-01)
December 18, 2000	Amendment #98 (Protocol Amendment)	New Protocol, Phase 1 Protocol PALO-99-34
December 20, 2000	Amendment #99 (Protocol Amendment)	Now investigators, Phase 3 Protocols PALO-99-03, PALO-99-04- PALO-99-05, and PALO-99-06
December 21, 2000	Telephone to Melodi McNeil	Feasibility of face-to-face CMC strategy meeting at FDA instead of teleconference at same date/time as scheduled FDA teleconference
December 26, 2000	Fax from FDA	FDA fax confirming (1) Pediatric protocol teleconference February 8, 2001, and (2) CMC Strategy meeting January 30th instead of a teleconference
January 2, 2001	Amendment #100 (Protocol Amendment)	Change in Protocols, Protocol Amendment No. 3 to Phase 3 Clinical Protocols PALO-99-03, PALO-99-04, PALO-99-05, and PALO-99-06

January 16, 2001	Amendment #101 (Reply to FDA request for information)	List of Sponsor's attendees and specific questions for CMC Strategy meeting, 30 January 2001
January 17, 2001	Telephone to Melodi McNeil	Follow-up to assure FDA receipt of list of Sponsor's attendees and list of specific, questions/salient points in preparation for the FDA CMC Strategy meeting 30 January.
January 22, 2001	Amendment #102 (Reply to FDA request for information)	List of Sponsor's attendees and specific questions for the Pediatric Protocol PALO-99-07 Teleconference on 8 February 2001
January 23, 2001	Telephone to Helen Wilson	Diskette of FDA-Requested Sponsor's Attendees and Specific Questions for the Pediatric Protocol PALO-99-07 teleconference scheduled for Thursday S February 2001, 9:30-11 AM East Coast time

January 25, 2001	Amendment #103 (New Investigators)	Protocol Amendment, New Investigators, Phase 3 Protocols PALO-99-03, PALO-99-04, PALO-99-05 and PALO-99-06
January 31, 2001	Letter from Dr. Talarico	FDA letter from Dr. Talarico dated 31 Jan 2001 (in electronic signature page) regarding juvenile rat to data – FDA recommendation that – 07 patients be evaluated for ophthalmic function
February 7, 2001	Telephone to Melodi McNeil	Possible cancellation of FDA teleconference on 8 February 2001
February 8, 2001	Telephone to Melodi McNeil	FDA agreement with Helsinn's replies (submitted in IND Serial #96) to FDA's comments and request (FDA letter, 26 Sept 2000) regarding the PALO-99-07 pediatric protocol, and agreement to cancel the FDA/Helsinn Pediatric Protocol teleconference

		scheduled for 8 Feb 2001
February 21, 2001	Telephone to Melodi McNeil	Notification that the number of survivors in the high dose female group in the PALO-98-03 rat carcinoginicity study reached 20 on Feb 20, 2001, week 95 of the study, and request for FDA guidance
February 21, 2001	Amendment #104 (Pharmacology /Toxicology)	Rat Carcinogenicity Study PALO-98-03, Twenty Remaining Survivors in High Dose Female Group - Request for Guidance
February 22, 2001	Telephone from Melodi McNeil	Resuming treatment in the high dose female group, in the Palonosetron rat carcinogenicity study until 20% of the group (n-13) remains as survivors, then discontinue treatment, do not kill the animals, and allow the group to proceed to the end of the 104 week study

February 23. 2001	Telephone to Melodi McNeil	Resumption of treatment administration to high dose female rats in the PALO-98-03 rat carcinogenicity study
February 27, 2001	Amendment #105 (New Investigator)	Protocol Amendment, New Investigators, Phase 3 Protocols PALO-99-03, PALO-99-04, PALO-99-05, and PALO 99-06
February 27, 2001	Letter from FDA	FDA minutes of Palonosetron NDA CMC strategy meeting held January 30, 2001

SECOND APPENDIX

To an Agreement between HELSINN HEALTHCARE SA and MGI PHARMA INC. dated April 6th, 2001

PATENTS

US Patent "Tricyclic 5-HT, receptor antagonist?

Patent Number 5,202,333

Issued: April 13, 1993

Application Number: 7-704,565

Filed: May 22, 1991

Expected Expiry Date: May 22, 2011

THIRD APPENDIX

To an Agreement between HELSINN HEALTHCARE SA and MGI PHARMA dated April 6th, 2001

THE PRODUCTS.

Qualitative description of the Products as submitted to the United States Food and Drug Administration under TNT 39,797 Amendment # 64 and to the Therapeutic Products Programme in Canada under IND 9427-H0836-21C

1. Palonosetron HCI Intravenons injection is supplied as a sterile, isotonic solution in 5 ml Type 1 clear glass vials each containing 5 ml of product. The product is clear and colorless solution, and contains the equivalent of either 0.05 mg/mL or 0.15 mg/mL of Palonosetron free base. The formulation also contains mannitol as a tonicifying agent, edetate disodium as a chelating agent and citrate buffer to maintain the pH of the solution at the target pH of 5 (+/- 0.5).

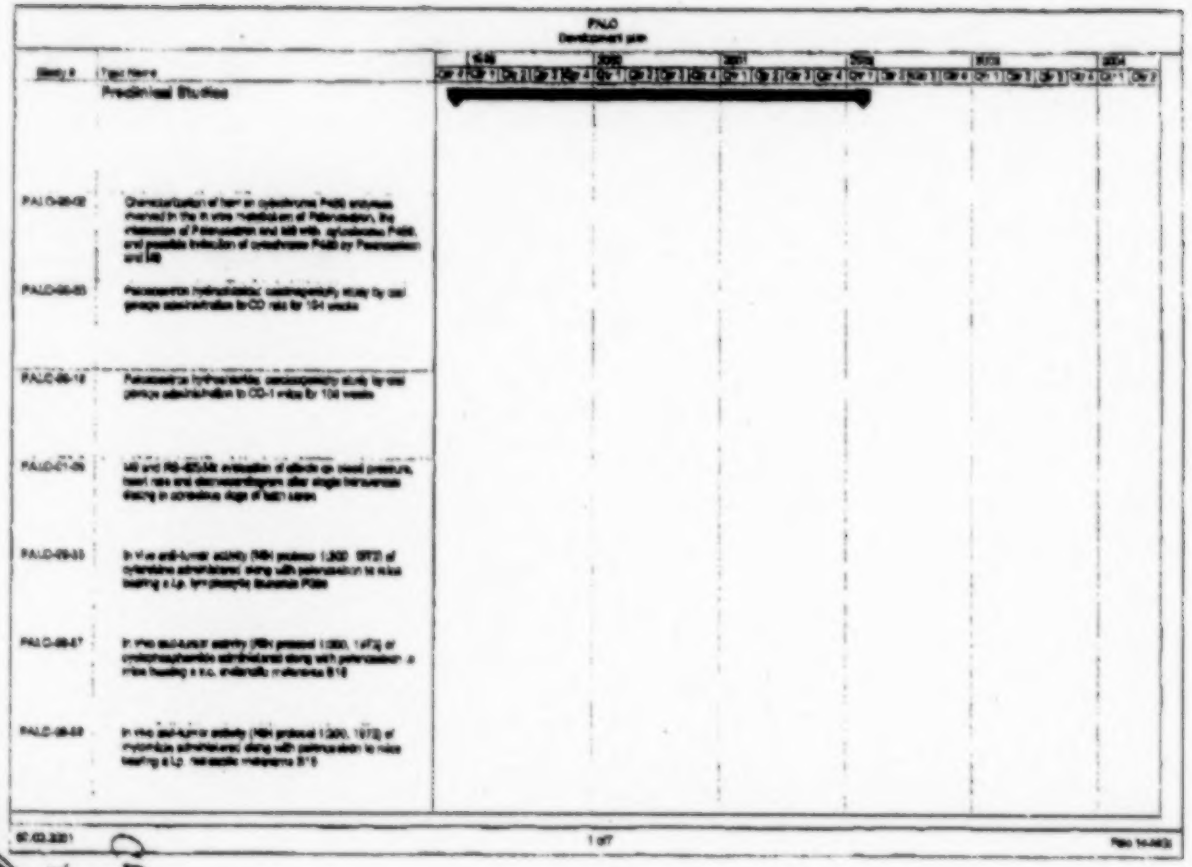
2. The product is terminally sterilized.

FOURTH APPENDIX

To an Agreement between HELSINN HEALTHCARE SA and MGI PHARMA dated April 6th, 2001

DEVELOPMENT CHART

See enclosed document, consisting of 7 pages.

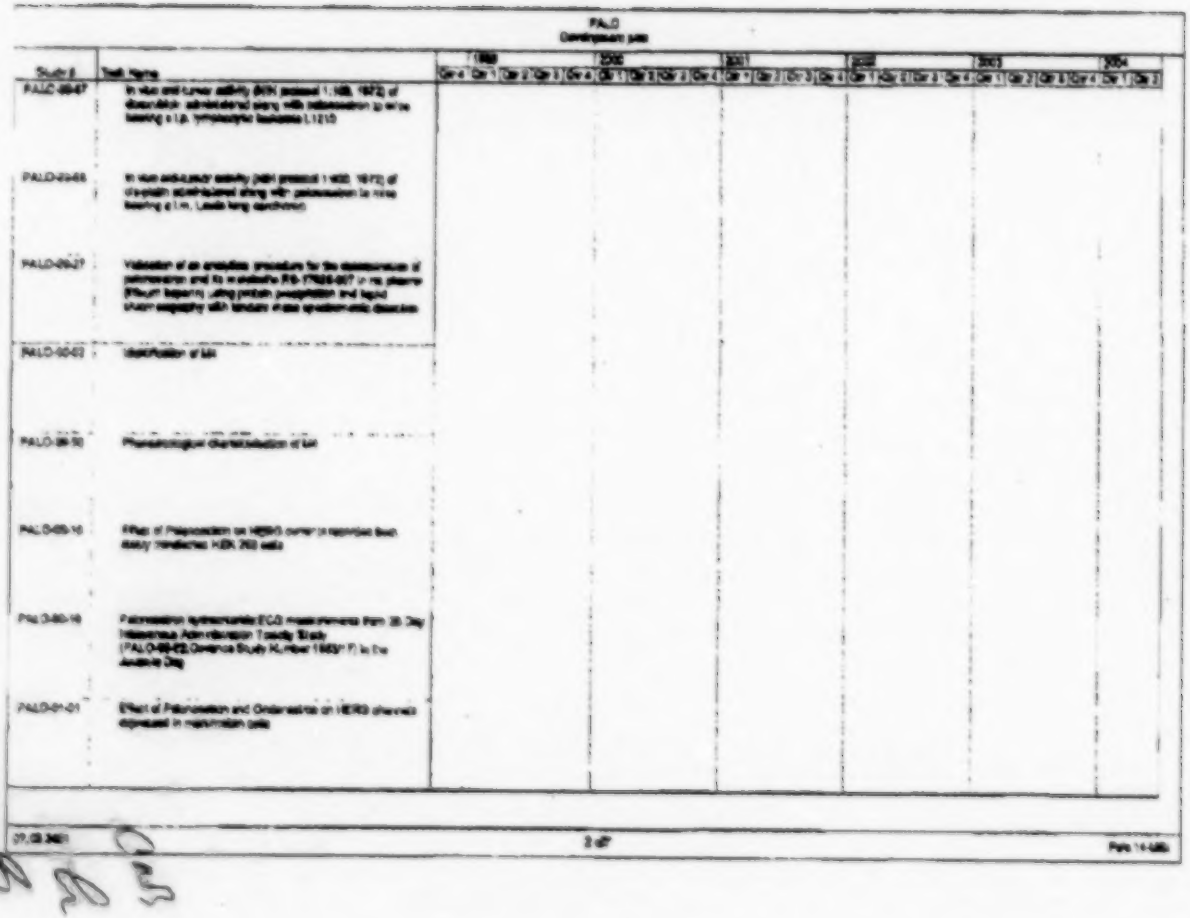


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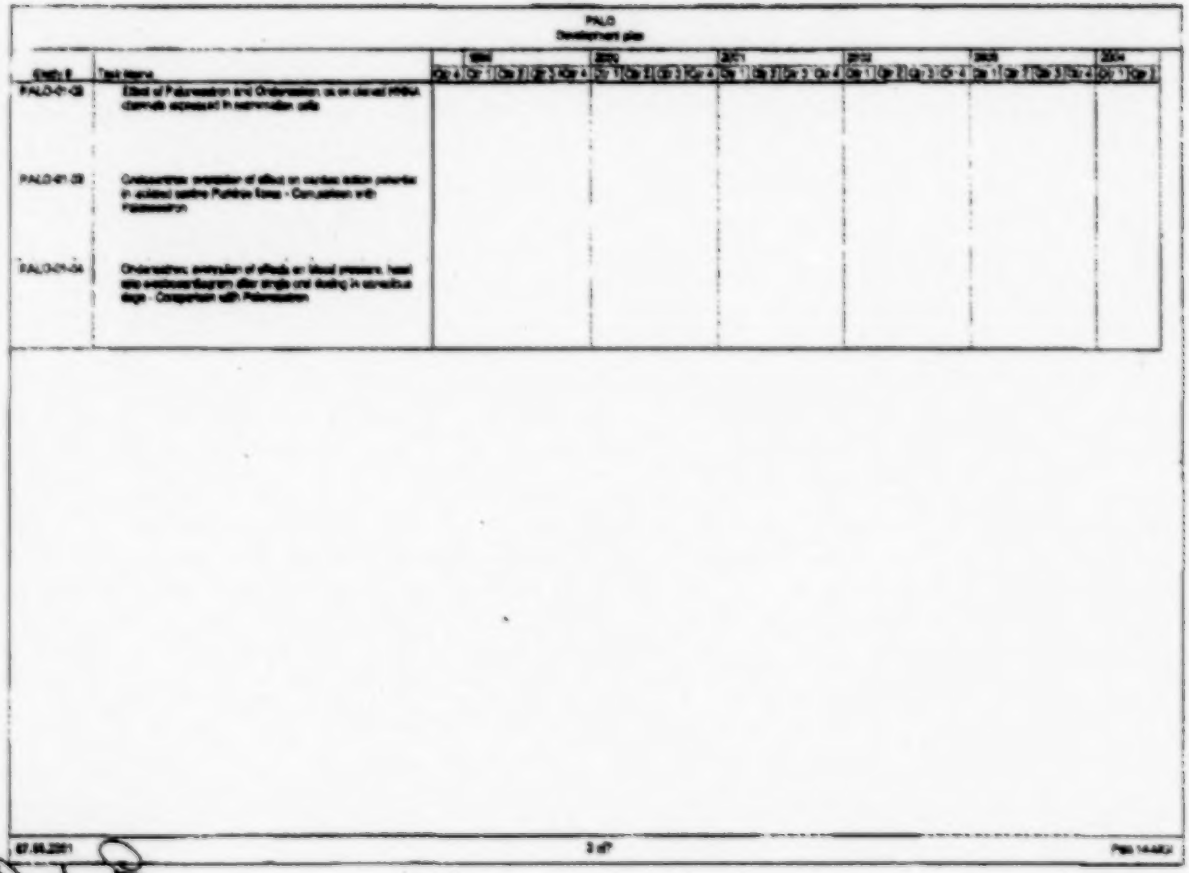
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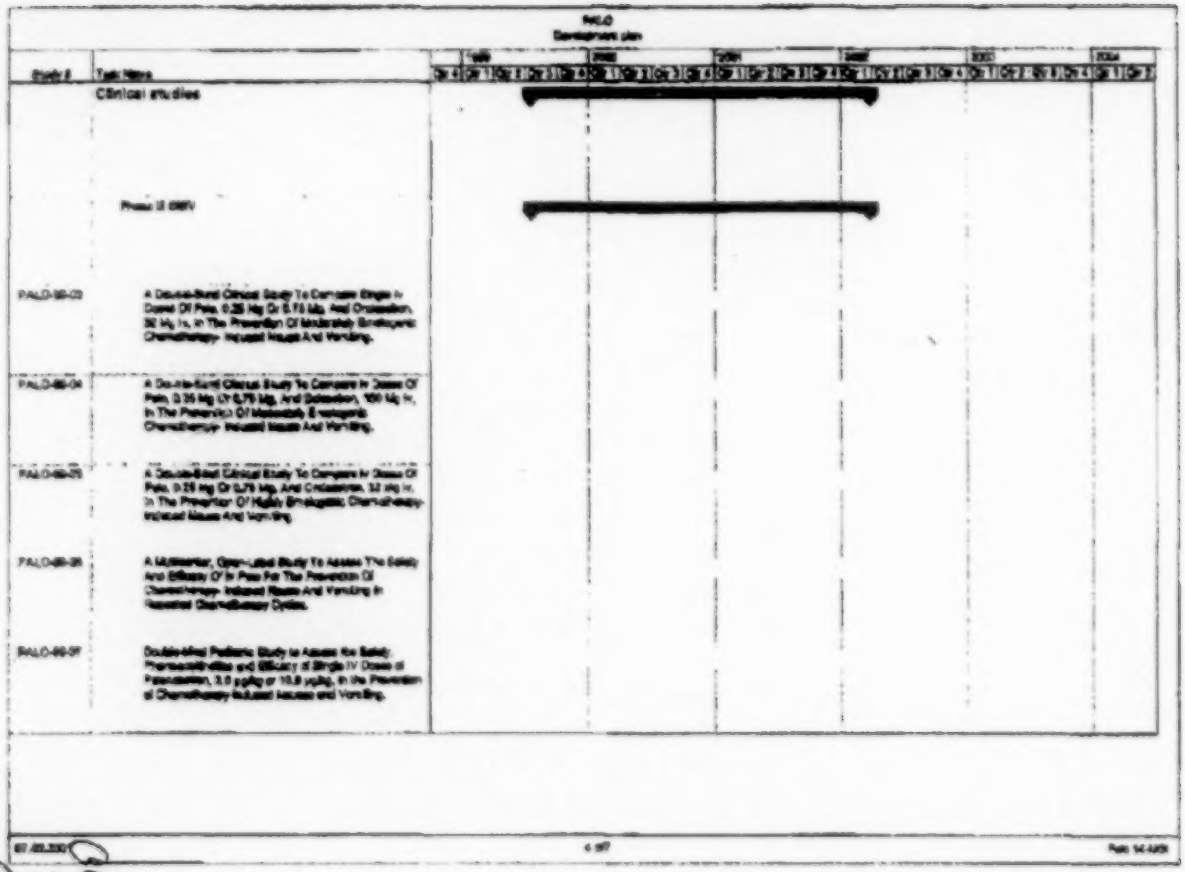


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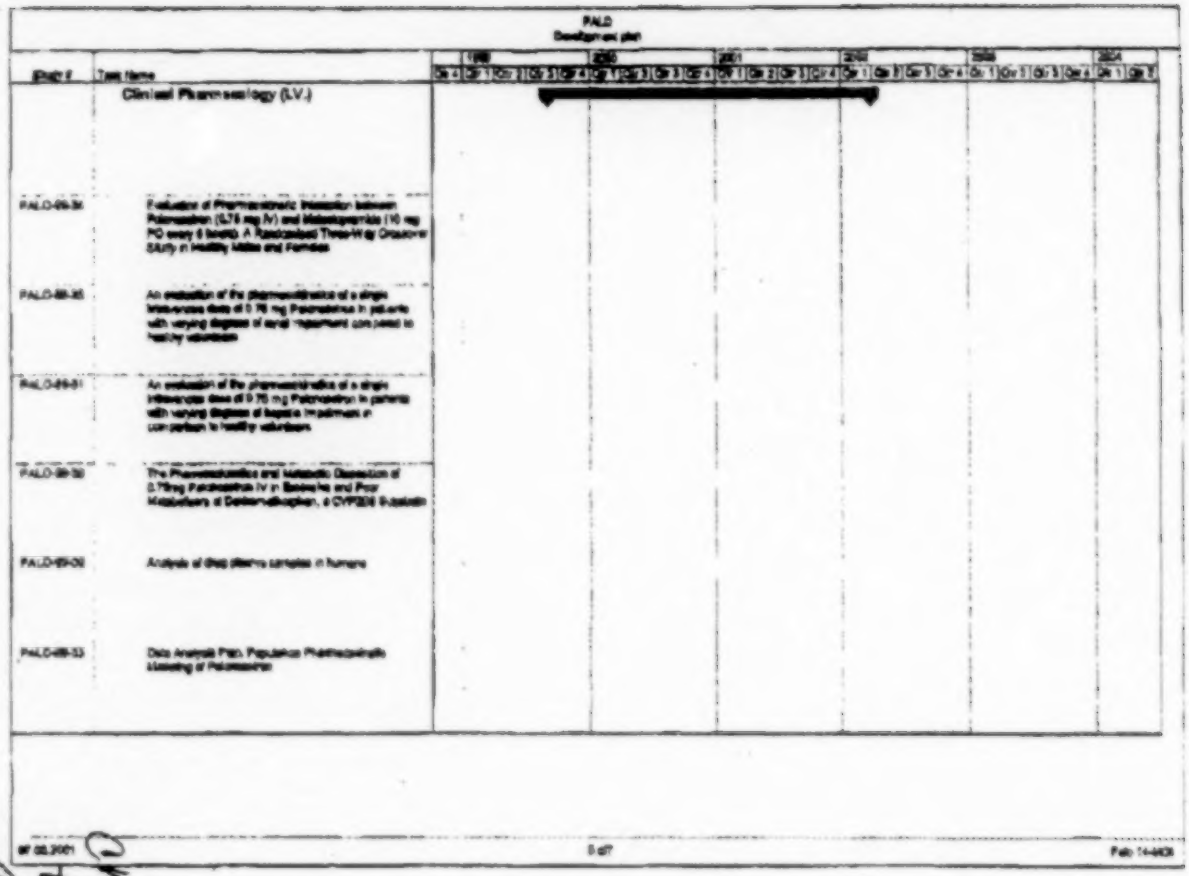
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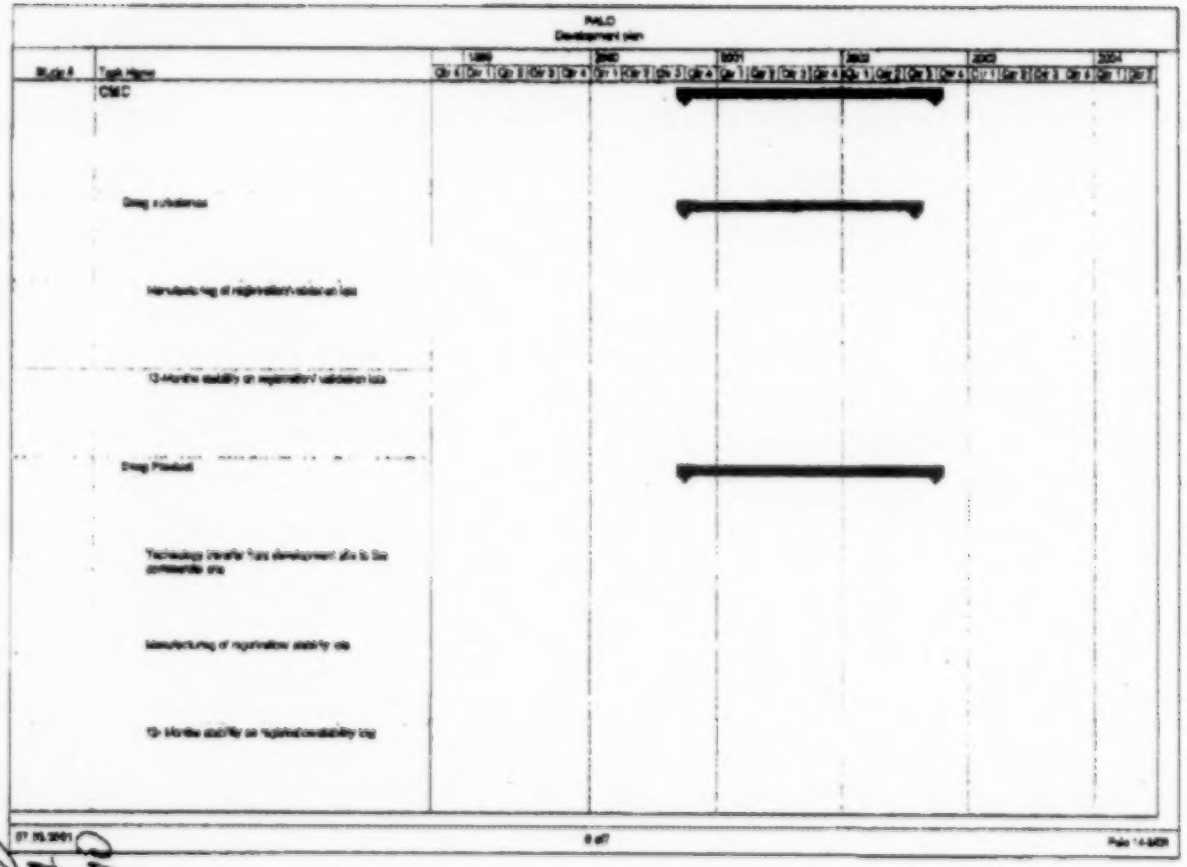
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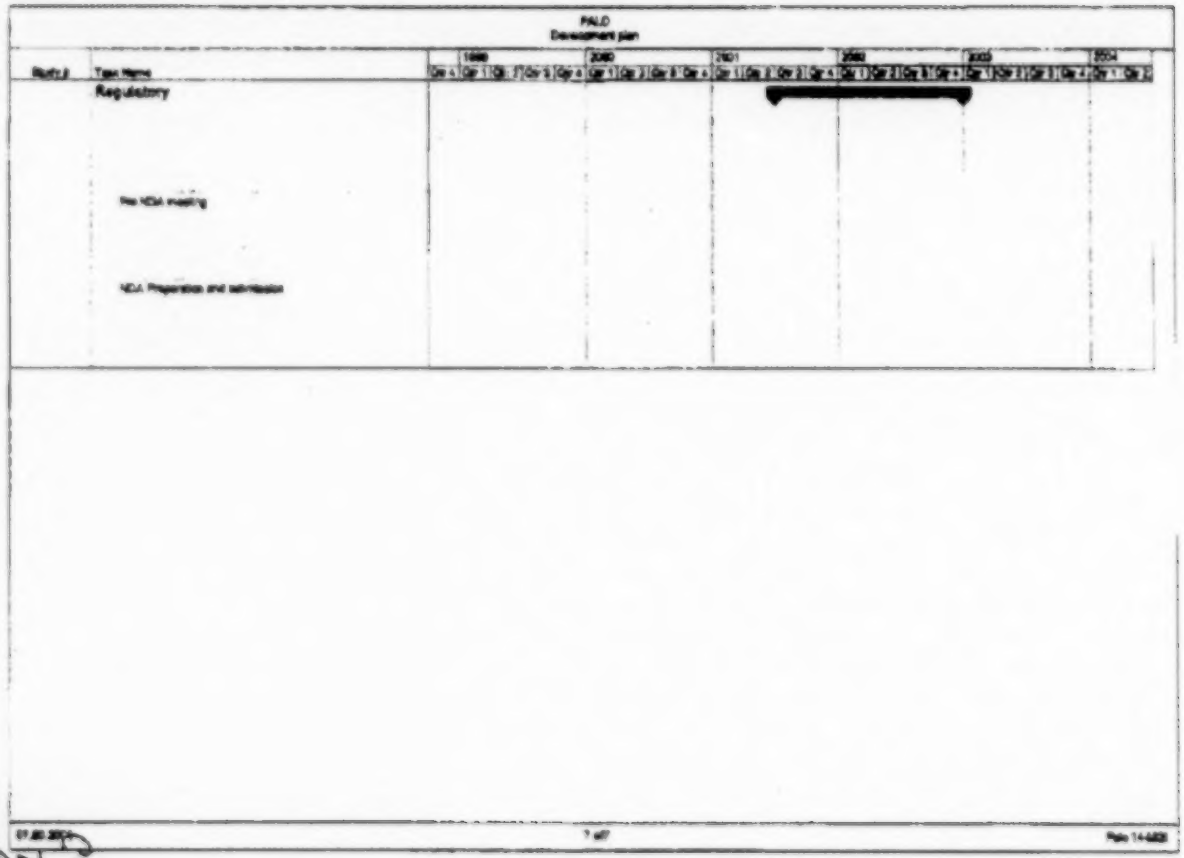
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HIGHLY CONFIDENTIAL - OUTSIDE COUNSEL EYES ONLY



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FIFTH APPENDIX

To an Agreement between HELSINN HEALTHCARE SA and MGI PHARMA dated April 6th, 2001

HHC's POST-REGISTRATION REGULATORY ACTIVITIES

With reference to Article 4.5, the regulatory activities specifically listed hereunder shall be performed and carried out directly by HHC:

1. To pay the annual user fees for the maintenance of the drug product authorization in the Territory;

2. To update the authorization with new safety information that may affect the statement of contraindications, warnings, precautions, or adverse reactions in the approved labeling;

3. To comply with Good Manufacturing Practice regulations in 21 CFR Parts 210, 211;

4. To comply with applicable Labeling regulations in 21 CFR Part 20];

5. To comply with regulations for making changes in the product authorization in 21 CFR 3I4.7I;

6. To inform FDA of any communication relevant to the drug product received by authorities other thao in the Territory having impact in the Territory.

SIXTH APPENDIX

To an Agreement between HELSINN HEALTHCARE SA and MGI PHARMA INC. dated April 6th, 2001

ADVERSE EVENTS REPORTING

See enclosed document.

Provisions For The Exchange Of Safety Data With Commercial Partners

1. GENERAL

1.1 Each of HHC's Affiliated Company/Partner designates a qualified person who is the reference person for drug safety and will ensure that the local legal requirements for Adverse Events reporting are met in the territory of his/her responsibility. Any change in this position is to be notified by each of HHC's Affiliated Company/Partner within 15 calendar days to the Drug Safety Unit of HHC (hereinafter "HHC/DSU").

1.2 All adverse events should be available in one single point. The partner agrees that all safety data/cases involving the Product are stored in the Helsinn Healthcare Database as the reference global database. The partner has to process all local cases using its own database.

2. DATA PROCESSING AND EXCHANGE PROCEDURES

2.1 Adverse Event

For the purpose of this document, an adverse Event or Adverse Experience (AE) is defined as:

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a casual relationship with this treatment.

An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, For example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

This definition includes intercurrent illnesses or injuries, exacerbation of pre-existing conditions, and adverse events occurring as a result of drug withdrawal, abuse, misuse or overdose. Adverse events observed during all periods of a clinical trial are to be recorded, including adverse events occurring during a period without trial medication. This also includes adverse events which are reported after a patient has completed the clinical study. Therapeutic failures during clinical trials are not considered to be adverse events.

Adverse Drug Reaction (ADR) / Adverse Reaction

Adverse drug reaction in this context is considered as synonymous with adverse reaction and suspected adverse drug reaction. Adverse drug reaction means a reaction which is harmful and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or treatment of disease or the modification of physiological function.

A reaction, contrary to an event, is characterised by the fact that a causal relationship between the drug and the occurrence is suspected, i.e. judged possible by the reporting or a reviewing health-care professional. If a reaction is spontaneously reported by a health-care professional, this usually implies a positive judgement from the reporter unless the reporter explicitly gives a negative judgement on the causal relationship.

Serious Adverse Reaction

This includes an adverse reaction which falls into one or more of the following categories:

fatal

life-threatening

results in persistent or significant disability/ incapacity

results in or prolongs hospitalisation.

This also includes congenital anomalies/birth defects and serious adverse clinical consequences associated with use outside the terms of the Summary of Product Characteristics (SPC) (including, for example, prescribed doses higher than those recommended), overdoses or abuse.

Medical judgement should be exercised in deciding whether a reaction is serious in other situations. Important adverse reactions that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the patient should be considered as actions.

2.1.1 Individual reporting of aft serious Adverse Events (AEs), irrespective of the source (e.g. spontaneous reports, Clinical Trials, literature, Regulatory Authorities), must be processed and transmitted by CIOMS form using the dedicated fax line by the Partner to HHC/DSU within 7 (seven) calendar days, after determination that the minimal criteria to handle the case have been met.

2.1.2 Reports (CIOMS form) as complete as possible for all non-serious AEs must be processed and forwarded to HHC/DSU on a monthly basis.

2.1.3 As regards. Clinical Trials, the "end of study safety report" should be sent to HHC/DSU.

2.1.4 The Partner is expected to follow up all serious AEs. Follow-up information (relevant medical information or any information affecting the case assessment) shall be transmitted where available in

the same manner as the initial information as described above (within seven calendar days).

2.1.5 All the US serious cases will be assessed and approved by HHC/DSU within 4 (four) calendar days.

2.1.6 All other serious cases (non-US) will be processed by HHC/DSU within 10 (ten) calendar days and CIOMS form will be transmitted to Partner. Tice eases have to be inserted in the local database-

2.1.7 The Partner is responsible for the submission to the authorities according to local time-frame of all relevant cases-

2.1.8 HHC/DSU is responsible for the preparation of the periodic safety update report (PSUR).

2.1.9 A PSUR will be prepared on a six monthly basis using the ICH format and will be distributed by HHC/DSU to all of HHC's Affiliated Companies and Licensces world-wide.

2.1.10 The Partner is responsible for the preparation and submission of periodic reports as required by local regulations. Any said report must be approved by HHC/DSU before notification, said approval to be considered as tacitly given in the absence of any communication by HHC within fifteen calendar days of receipt of the report.

3. LABELLING

3.1 HHC/DSU prepares a Company Core Data Sheet (CCDS) which covers material related to safety, indication, dosing, pharmacology and other information concerning the product.

3.2 It is therefore advisable that all HHC Affiliates/ Partners refer to the CCDS and maintain the Summary of Product Characteristics (SPC) and leaflets as

close as possible to the "reference document" (CCDS) in the different countries and for the different companies marketing the products under HHC's license all over the world. Changes specifically requested by local Regulatory Authorities, if any, are inserted in the SPCs and leaflets and HHC/DSU has to be informed of the changes. A copy of the revised SPC/leaflet will be sent to HHC/DSU.

4. OTHER SAFETY DATA

4.1 The partners have to agree mutually exchange of information regarding any safety aspects of the Products. This includes information on any restrictions given by the Health Authority to the Product and warning and contraindications on product information texts (SPC, leaflets).

5. REPORTING TO THE REGULATORY AUTHORITIES

5.1 Each Partner is responsible locally for safety monitoring, management and reporting of individual case reports in an expedited manner, when applicable, and for the submission of the HHC Periodic Safety Update Reports (PSUR) to the relevant Regulatory Authorities in accordance with the current regulation of each country.

5.2 If it is deemed necessary the PSUR provided by HHC/DSU on a six monthly basis will be completed/ integrated with additional data by the Partner to comply with local requirements and after agreement with HHC/DSU.

5.3 Copy of any written communication and document submitted to the Regulatory Authorities, where different from the PSUR provided by HHC, must be forwarded to HHC, possibly before submitting

it to the Regulatory Authority for HHC's approval, which shall be considered as tacitly given in the absence of any communication by HHC within fifteen calendar days of receipt of the draft.

Reference address for any safely information transmission is the following;

Drug Safety Unit

MEDICAL AFFAIRS DIVISION HELSINN
HEALTHCARE SA
P.O. Box 357
6915 Pambio-Noranco
phone +41/91 985 21 21
Fax +41/91 985 21 71

SEVENTH APPENDIX

To an Agreement between HELSINN HEALTHCARE SA and MCA PHARMA INC dated April 6th, 2001

PRODUCTS RECALL PROCEDURE

See enclosed documents.

Definition Of Responsibilities For Handling Of Product Complaints, NDA-Field Alerts, Market Withdrawals, Product Recall

1. COMMUNICATION/RESPONSIBILITY/ AUTHORITY

Each Party shall promptly inform the other Party of any event, including but not limited to Product Complaint or NDA-Field Alerts, that might require the necessity of initiating a Product Recall or Market Withdrawal.

HHC and MGI shall co-operate in good faith to decide whether or not such actions need to be implemented. In case of disagreement, the final decision will be to proceed as long as one of the two parties decides to effect the Product recall or the Market Withdrawal.

2. COORDINATION OF PRODUCT RECALL OR MARKET WITHDRAWAL ACTIVITIES

In any event, with respect to any Recall, Product Withdrawal, or Field Correction. MGI shall make all contacts with the FDA in accordance with the terms and conditions of this Agreement and shall be responsible for coordinating all the necessary activities in connection with such Recall, Product Withdrawal or Field Correction.

3. RECALL TERMINATION

MGI shall provide HHC with a document that demonstrates that it is reasonable to assume that the Product subject of the recall or market withdrawal has been removed and proper disposition or corrections have been made.

4. LIABILITY FOR RECALL. COSTS

If a Recall, Product Withdrawal or Field Correction is necessary for any reason, HHC and MGI shall each bear the costs of the recall in proportion to each Party's responsibility for the error necessitating the recall, including but not limited to costs associated with defending or settling claims for product liability, receiving and administering the recalled Product and notification of the recall to those persons whom MGI deems appropriate.

5. PROCEDURES

Procedures regulating the activities to be performed for managing Product Complaints, NDA-Technical Field Alert Report, Product Recall and Market Withdrawals shall be mutually developed, agreed and approved between MGI and HHC.

6. CONFIDENTIALITY

Without prejudice to reporting obligations towards Regulatory Authorities provided for in this Appendix and/or established by applicable laws and regulations, all communications relating to any recall, product withdrawal or field correction shall be kept confidential in accordance with the provisions of Article 14 of this Agreement

EIGHT APPENDIX

To an Agreement between HELSINN HEALTHCARE SA and MGI PHARMA INC- dated April 6th, 2001

ESCROW AGREEMENT

See enclosed document

ESCROW AGREEMENT

Pursuant to this Escrow Agreement, dated _____ (the "Agreement"), HELSINN HEALTHCARE SA and MGI PHARMA, INC. (the "Parties") hereby establish Escrow Account No. _____ (the "Account") with U.S. Bank Trust National Association, a national banking association (the "Agent"), to be maintained and administered for the purposes described in Schedule I attached hereto in accordance with the following terms and conditions:

The Parties are party to a Licence Agreement of even date herewith pursuant to which MGI PHARMA, INC. is obligated to make certain milestone payments to Helsinn Healthcare SA.

The funds and/or property described on Schedule I attached hereto and incorporated herein (the "Asset?) shall be deposited in the Account upon delivery thereof to the Agent at its office in St. Paul, Minnesota by the depositors identified below (the -Depositors") no later than 15 days from the date of this Agreement. The Agent is hereby authorized and directed by each of the Parties, as their escrow agent, to hold, deal with and dispose of the Assets as provided in the Instructions set forth in Schedule H attached hereto and incorporated herein; subject, however, to the terms and conditions set forth below, which in all events, shall govern and control over any contrary or inconsistent provisions contained in Schedules I or II attached hereto.

1. Agent's Duties. The Agent shall hold, deal with and dispose of the Assets deposited to the Account in accordance with the provisions set forth in this Agreement and the Schedules attached hereto. The

Agent's duties and responsibilities shall be limited to those expressly set forth in this Agreement, and the Agent shall not be subject to, or obliged to recognize, any other agreement between any or all of the Depositors or any other persons even though reference thereto may be made herein; provided, however, that this Agreement may be amended at any time or times by an instrument in writing signed by the Parties hereto and the Agent. The Agent shall not be subject to or obligated to recognize any notice, direction or instruction of any or all of the Depositors or of any other person, except as expressly provided for and authorized in Schedule 11.

2. Court Orders or Process. If any controversy arises between the Parties to this Agreement, or with any other party, concerning the subject matter of this Agreement, its terms or conditions, the Agent will not be required to determine the controversy or to take any action regarding it. The Agent may hold all documents and funds and may wait for settlement of any such controversy by final appropriate legal proceedings or other means. In such event, the Account shall collect interest in accordance with Section 4 and 6 hereof. The Agent is authorized, in its sole discretion, to comply with orders issued or process entered by any court with respect to the Account, the Assets or this Agreement, without determination by the Agent of such court's jurisdiction in matter. if any Assets are at any time attached, garnished, or levied upon under any court order, or in ease the payment, assignment, transfer, conveyance or delivery of any such property shall be stayed or enjoined by any court order, or in case any order, judgment or decree shall be made or entered by any court affecting such property or any part thereof, then in any such events the Agent is authorized, in its sole discretion, to rely

upon and comply with any such order, writ, judgement or decree which it is advised by legal counsel of its own choosing is binding upon it; and if the Agent complies with any such order, writ, judgment or decree, it shall not be liable to any of the Depositors or to any other person, firm or corporation by reason of such compliance even though such order, writ, judgment or decree may be subsequently reversed, modified, annulled, set aside or vacated.

3. Agent's Actions and Reliance. The Agent shall not be personally liable for any act taken or omitted by it hereunder if taken or omitted by it in good faith and in the exercise of its own best judgment, The Agent shall also be fully protected in relying upon any written notice, instruction, direction, certificate or document signed by each of the Parties which in good faith it believes to be genuine.

4. Collections. Unless otherwise specifically indicated in Schedule 11, the Agent shall proceed as soon as practicable to collect any cheeks, interest due, matured principal or other collection items with respect to Assets at any time deposited in the Account. All such collections shall be subject to the usual collection procedures regarding items received by the Agent for deposit or collection- The Agent shall not be responsible for any collections with respect to Account Assets if the Agent is not registered as record owner thereof or otherwise is not entitled to request or receive payment thereof as a matter of legal or contractual right. All collection payments shall be deposited to the Account, except as otherwise provided in Schedule 11. Agent shall not be required or have a duty to notify anyone of any payment or maturity under the terms of any instrument, security or obligation deposited in the Account, nor to take any

legal action to enforce payment of any check, instrument or other security deposited in the Account. The Account is a safekeeping escrow account, and no interest shall be paid by Agent on any money deposited or held therein, except as provided in Section 6 hereof

5. Agent Responsibility. The Agent shall not be liable to any Party for consequential damages (including, without limitation lost profits), losses or expenses in performing its duties under this Agreement, except for gross negligence or willful misconduct on the part of the Agent. The Agent shall not be responsible or liable for the sufficiency or accuracy of the form, execution, validity or genuineness of documents, instruments or securities now or hereafter deposited in the Account, or of any endorsement thereon, or for any lack of endorsement thereon, or for any description therein. Registered ownership of or other legal title to Assets deposited in the Account shall be maintained in the name of the Agent. The Agent may maintain qualifying Assets in a Federal Reserve Bank or in any registered clearing agency (including, without limitation, the Depository Trust Company) as the Agent may select, and may register such deposited Assets in the name of the Agent or its agent or nominee on the records of such Federal Reserve Bank or such registered clearing agency or a nominee of either. The Agent shall not be responsible or liable in any respect on account of the identity, authority or rights of the persons executing or delivering or purporting to execute or deliver any such document, security or endorsement or this Agreement.

6. Investments. All monies held in the Account shall be invested by the Agent in its name or its nominee's name, in such instruments or securities as expressly authorized in Schedule III. The Agent may

sell securities (including shares or units in any money market mutual funds) to make any payments from the Account as provided hereunder. The Agent shalt not be responsible for the selection, quality or maturity of such investments, or for the timely reinvestment of interest or maturity proceeds thereof except as provided in the immediately following paragraph.

Monies credited to any account or fund maintained hereunder which are uninvested pending disbursement or receipt of proper investment directions or as directed herein, may be deposited to and held in a non-interest bearing demand deposit account established with the Commercial Banking Department of the Agent or with any bank affiliated with the Agent, without the pledge of securities to or other collateralization of such deposit accounts.

The Parties acknowledge and agree that the Agent is authorized to invest from or through its trust department or U.S. Bank National Association or any other bank affiliated with the Agent through common cannel by U.S. Bancorp.

7. Notices/Directions to the Agent. Notices and directions to the Agent from Depositors, or from other persons authorized to give such notices or directions as expressly set forth in Schedule Il, shall he in writing and signed by an authorized representative as identified pursuant to Schedule Il, and shall not be deemed to be given until actually received by Agent's employee or officer who administers the Account. The

Agent shall not be responsible or liable for the authenticity or accuracy of notices or directions properly given hereunder if the written form and execution thereof on its face purports to satisfy the requirements applicable thereto as set forth in

Schedule 11, as determined by Agent in good faith without additional confirmation or investigation.

8. Books and Records. The Agent shall maintain books and records regarding its administration of the Account, and the deposit, investment, collections and disbursement or transfer of Assets, shall retain copies of all written notices and directions sent or received by ii in the performance of its duties hereunder, and shall afford each Depositor and each Party reasonable access, during regular business hours, to review and make photocopies (at Depositor's cost) of the same.

9. Disputes Among Depositors and/or Third Parties. In the event the Agent is notified of any dispute, disagreement or legal action between or among any of the Depositors, and/or any third parties, relating to or arising in connection with the Account, the Assets or the performance of the Agent's duties under this Agreement, the Agent shall be authorized and entitled, subject to Section 2 hereof, to suspend further performance hereunder, to retain and hold the Assets then in the Account and take no further action with respect thereto until the matter has been fully resolved, as evidenced by written notification signed by the Parties and any other parties to such dispute, disagreement or legal action.

10. Notice by Agent. Any notices which the Agent is required or desires to give hereunder to any of the Parties shall be in writing and may be given by mailing the same to the address of the Party indicated below (or to such other address as said Party may have theretofore substituted therefor by written notification to Agent), by United States certified or registered mail, postage prepaid. Whenever under the terms

hereof the time for Agent's giving a notice or performing an act falls upon a Satarday, Sunday, or holiday, such time shall be extended to the next business day.

If to MGI PHARMA, INC.:

MGI PHARMA, Inc.
6300 West Old Shakopee Road
Suite 110
Bloomington, MN 55438
USA
Attention: Manager, Legal Affairs
Facsimile: (952) 346-4800

If to Helsinn Healthcare SA

Helsinn Healthcare SA
P.O. Box 357
6915 Pambio-Noranco
Switzerland
Attention: Legal Department
Facsimile: 01141919932122

11. Legal Counsel if the Agent believes it to be reasonably necessary to consult with counsel concerning any of its duties in connection with the account or this Agreement, or in case the Agent becomes involved in litigation on account of being the Agent hereunder or on account of having received property subject hereto, then in either case, its costs, expenses, and reasonable attorney's fees shall he paid by the Parties in equal amounts.

12. Agent Compensation. The Agent shall he paid by MGI PHARMA, INC. a fee for its services as set forth on Schedule IV attached hereto and incorporated herein, and reimbursed by MGI PHARMA, INC. for its reasonable costs and expenses incurred, an invoice of which such costs and expenses shall be provided to the

Parties. If the Agent's fees, or reasonable costs or expenses, provided for herein, are not promptly paid fifteen days following receipt of written notice of an overdue payment, the Agent shall have the right to sell such portion of the Assets held in the Account as necessary and reimburse itself therefor from the proceeds of such sale or from the cash held in the Account. In the event that the conditions of this Agreement are nut promptly fulfilled, or if the Agent, at the written request of the Parties, renders any service not provided for in this Agreement, or if the Parties request, in writing, a substantial modification of its terms, or if the Agent is made a party to, or intervenes in, any litigation pertaining to this Agreement, the Agent shall, upon the written approval of the parties for such costs, be reasonably compensated for such extraordinary services and reimbursed for all reasonable costs, reasonable attorney's fees, and expenses occasioned by such default, delay, or litigation and the Agent shall have the right to retain only the equivalent amount of such unpaid costs and expenses from the Assets at such time held by the Agent io the Account until such compensation, fees, casts, and expenses are paid. These sums shall be paid upon demand by the Parties in equal amounts. The Depositors and their respective successors and assigns agree jointly and severally to indemnify and hold the Agent harmless against any and all losses, claims, damages, liabilities, and expenses, including reasonable costs of investigation, reasonable counsel fees, and disbursements that may be imposed on the Agent or incurred by the Agent in connection with the performance of his/her duties under this Agreement, including but not limited to any litigation arising from this Agreement or involving its subject matter, except for losses, claims, damages, liabilities, and expenses

arising from the gross negligence or willful misconduct on the part of the Agent. The Agent shall have a first lien on the property and papers held under this Agreement for such compensation and expenses.

13. Agent Resignation. It is understood that the Agent reserves the right to resign at any time by giving written notice of its resignation, specifying the effective date thereof, to the Depositors, which such effective date shall be at least 30 days from the date of the written notice. Within 30 days after receiving the aforesaid notice, the Depositors agree to appoint a successor escrow agent reasonably satisfactory to each of the Parties to which the Agent may transfer the Assets then held in the Account, less its unpaid fees, costs and expenses. The Agent shall promptly transfer the Assets then held in the Account upon receipt of the notice of appointment of the successor escrow agent. If a successor escrow agent has not been appointed and has not accepted such appointment by the end of the 30-day period, the Agent may apply to a court of competent jurisdiction for the appointment of a successor escrow agent, and the costs, expenses and reasonable attorney's fees which the Agent incurs in connection with such a proceeding shall be paid by MGI PHARMA, INC.

14. Escrow Termination. If, as provided in Schedule II, this Agreement shall not have previously terminated and a dispute, disagreement or legal action pursuant to Section 9 hereof has not commenced, then it shall automatically terminate on the second anniversary of the date of this Agreement, at which time the Assets, plus any interest earned thereon, then held in the Account, less the Agent's unpaid fees, costs and expenses shall be distributed in the following manner:

Returned to MGI PHARMA, INC. by wire transfer to:

US Bank Minnesota

601 Second Avenue South

Minneapolis, MN USA 55402

ABA# 0910-0002-2

FBO MGI PHARMA,

A/C# 1-702-2513-9162

15. Governing Law. This Agreement shalt be construed, enforced, and administered in accordance with the laws of the State of Minnesota.

16. Automatic Succession Any company into which the Agent may be merged or with which it may be consolidated, or any company to whom Agent may transfer a substantial amount of its Escrow business, shall be the Successor to the Agent without the execution or filing of any paper or any further act on the part of any of the Parties, anything herein to the contrary notwithstanding.

IN WITNESS WHEREOF, the parties have duly executed this Agreement as of the day and year first above written.

Name and Address	Signature and Title
Dr. Riccardo Braglia or	_____
	Managing Director
Dr. Enrico Braglia	_____
	Managing Director

HELSINN HEALTHCARE SA
P.O. Box 357
6915 Pambio-Horanco
SWITZERLAND

DEPOSITORS

Charles N. Blitzer or _____
Chief Executive Officer

Leon O. Moulder, Jr _____
Executive Vice President

MGI PHARMA, INC.
6300 West Old Shakopee Road
Suite 110
Bloomington, MN 55438-2318
USA

U.S. Bank Trust National Association, as Agent

By:_____

SCHEDULE
PURPOSE OF ESCROW

The purpose of this escrow arrangement is to provide for appropriate, timely payment of two milestone payments under the License Agreement between HELSINN HEALTHCARE SA and MGI PHARMA, INC. dated _____, 2001.

No later than 15 days from the date of execution of this Agreement, MGI PHARMA, INC. shall deposit $6,000,000 into the Account.

SCHEDULE II
INSTRUCTIONS OF DEPOSITORS

All escrow monies are to be invested as indicated on Schedule HI until disbursement is needed as follows:

$2 million is to be wired for the benefit of HELSINN HEALTHCARE SA six months after execution of this Agreement

$4 million is to be wired for the benefit of HELSINN HEALTHCARE SA upon confirmation that a Type B pre-NDA meeting related to palonosetron has occurred with the United States Food and Drug Administration. This confirmation may take the form of a copy of FDA's record of meeting attendees or a copy of FDA provided minutes from the meeting to be provided by representatives of either HELSINN HEALTHCARE or MGI PHARMA. Alternatively, written acknowledgment of the meeting's occurrence from one of the MGI PHARMA signatories to this escrow agreement may serve. The Parties shall give the Agent a joint written notice to such effect.

Wire transfers to HELSINN HEALTHCARE should be made using the following instructions:

UBS SA
Via Pretorio 9
CH-6901 Lugano
Swift UBSW CH ZH69A
A/C# 459.089.62L HELSINN

MGI PHARMA is entitled to all of the investment earnings of the escrowed assets, and any assets remaining after the disbursements listed above have been made will be paid for the benefit of MGI PHARMA, INC. to:

US Bank Minnesota
60I Second Avenue South
Minneapolis, MN USA 55402
ABA# 0910-0002.2 FBO
MGI PHARMA, INC.
A/C# 1-702-2513-9162

SCHEDULE III

In the absence of specific written direction to the contrary, you are hereby directed to invest and reinvest proceeds and other available monies in any of the following funds/deposits as permitted by the operative documents (SEE BELOW DESCRIPTION OF INVESTMENT VEHICLES AND FEE BASIS FOR EACH). Please mark one space with an X for the investment vehicle selection.

___ First American Treasury Obligations Fund (Class D)*

___ First American Government Obligations Fund (Class D)*

_X_ First American Prime Obligations Fund (Class D)*

___ First American Tax Free Obligation Fund (Class D)*

___ U.S. Bank Money Market Deposit Account**

*First American Funds:

SEE FIRST AMERICAN FUNDS, INC. PROSPECTUS WHICH HAS BEEN/OR WILL BE PROVIDED. NOTE THAT THE ABOVE FUNDS' INVESTMENT ADVISOR AND CUSTODIAN ARE SUBSIDIARIES OF U.S. BANCORP. SHARES OF THE FUNDS ARE NOT DEPOSITS OR OBLIGATIONS OF, OR GUARANTEED BY, ANY BANK INCLUDING U.S. BANK NATIONAL ASSOCIATION, U.S BANK TRUST NATIONAL ASSOCIATION, OR ANY OF THEIR AFFILIATES, NOR ARE THEY INSURED BY THE FEDERAL DEPOSIT INSURANCE CORPORATION, THE FEDERAL RESERVE BOARD OR ANY OTHER AGENCY. AN INVESTMENT IN THE FUNDS INVOLVES INVESTMENT RISK,

INCLUDING POSSIBLE LOSS OF PRINCIPAL. Neither U.S. Bank Trust nor U.S. Bank will vote proxies for the First American Funds. Proxies will be mailed to your designated voter.

Fee Basis; Approval of investment in any of these First American mutual funds includes approval of the fund's fees and expenses as detailed in the prospectus, including advisory and custodial fees and 12b-1 shareholder service expenses, which fees and expenses are paid to U.S. Flank Mist or U.S. Bank, subsidiaries of U.S. Bancorp.

**U.S. Bank Money Market Deposit Account

This fund is a bank time deposit of U.S. Bank National Association. The interest rate paid is the average of the Goldman ILA Prime Fund, the Shearson Temp and Federated Prime Funds. Selection includes authorization to invest in deposits of U.S. Bank National Association or any other bank affiliated with U.S. Bank Trust National Association through common control by U.S. Bancorp.

Fee Basis: In selecting the U.S. Bank Money Market Deposit Account, authorization is given to deduct an administrative management fee of 40 basis points (.0040) (subject to change upon notice) against the average daily fund balances, netted from investment earnings or monies.

If U.S. Bank Trust National Association is directed, to invest available account monies pursuant to the operative documents, in a mutual fund not managed or sponsored by an affiliate of U.S. Bank Trust National Association, it may charge such fund, or the fund's investment manager, a fee for services for fund share accounting and administrative services, not to exceed 40 basis points (.0040) of 1 percent of the

account monies so invested in the fund. Payment of such service fees will not result in any increase in fees charged against the fund's assets or earnings above the fee and expense levels otherwise established and charged for the fund, as disclosed in the fund prospectuses.

SCHEDULE IV

Agent's Fees

All fees shall be paid by MGI PHARMA, INC. as follows:

Acceptance Fee: $ 1,250.00

(Includes review of Agreement and establishing procedures and controls)

First year's administrative fee:
(payable in arrears)

If all funds are invested in a Money Market Fund utilized by U.S. Bank Trust $ 1,500.00

If funds are invested other than above $ 2,000.00

Subsequent year administration fee: as above
(payable in arrears)

Charges

Disbursements (checks or wires) $20.00 Each

Fee for security transactions:

A. Settlement of trades in the open market at direction of customer $75.00 per buy or sale
$50.00 per maturity

B. Trading in authorized Money Market Funds utilized by U.S. Bank Trust as Prospectus or Schedule indicates

Out-of-Pocket Expenses: Billed at Cost

Expenses including but not limited to stationery, postage, telephone, insurance, shipping, Telex/ Telegram, services of outside counsel and agents. (Plus indirect out-of-pocket at 3% of administrative fee.)

Note: Charges for performing other escrow services not specifically covered in this schedule will be determined by an appraisal of the services rendered. The fees shown in this schedule may be increased annually.

NINTH APPENDIX

To an Agreement between HELSINN HEALTHCARE SA and MGI PHARMA INC. dated April 6th, 2001

MGI'S UNIT SALES BASE FORECASTS ANNUAL MINIMUM SALES

See enclosed document.

Ninth Appendix

Value $ (000's) and Units (000's)

1) USA HGE UNIT SALES FORECAST

	YEAR 1	YEAR 2	YEAR 3	YEAR 4	YEAR 5	YEAR 6	YEAR 7	YEAR 8	YEAR 9	YEAR 10
Units	118	298	662	875	785	666	549	434	391	212

2) USA ANNUAL MINIMUM SALES

Minimum annual sales	$ 11'123	$ 28'826	$ 65'915	$ 89'748	$ 82'906	$ 72'432	$ 60'902	$ 51'873	$ 46'014	$ 25'668

HIGHLY CONFIDENTIAL - OUTSIDE COUNSEL EYES ONLY

A01595

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TENTH APPENDIX

To an Agreement between HELSINN HEALTHCARE SA and MGI PHARMA INC. dated April 6th, 2001

PROMOTION AND MARKETING ACTIVITIES

See enclosed document.

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Tenth Appendix

$(000's)

USA MARKETING ACTIVITIES

	YEAR 1	YEAR 2	YEAR 3	YEAR 4	YEAR 5	5Y TOTAL	YEAR 6	YEAR 7	YEAR 8	YEAR 9	YEAR 10
Sales force expenses	$ 8750	$ 8750	$ 8750	$ 8750	$ 4375	$ 39375	$ 4375	$ 4375	$ 4375	$ 4375	$ 4375
Marketing expenses	$ 11700	$ 9000	$ 9000	$ 8000	$ 7000	$ 44000	$ 7000	$ 3000	$ 3000	$ 3000	$ 3000
Medical expenses	$ 400	$ 300	$ 250	$ 250	$ 250	$ 1450	$ 250	$ 250	$ 250	$ 250	$ 250
Total selling expenses	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Maximum sales force 40 full time sales representatives

Appropriate number of visits to key doctors as per the average of the market for each class of products

Participation to the major congresses in oncology (e.g. ASCO)

HIGHLY CONFIDENTIAL - OUTSIDE COUNSEL EYES ONLY

HELSN0138228

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EXHIBIT O

Supply and Purchase Agreement

between

HELSINN BIREX PHARMACEUTICALS LTD

and

MGI PHARMA, INC.

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THIS AGREEMENT (hereinafter called "Agreement") is effective as of this 6th day of April 2001 (hereinafter called "Effective Date"), between HELSINN BIREX PHARMACEUTICALS LTD, a corporation organized and existing under the law of the Republic of Ireland and having its registered office at Damastown, Mullhuddart, Dublin 15, Republic of Ireland (hereinafter called "HBP") of the one part, and MGI PHARMA, INC., a corporation organized and existing under the law of the state of Minnesota, United States of America and having its registered office at 6300 West Old Shakopee Road, Suite 110, Bloomington, MN 55438-2318, USA thereinafter called "MGI"), of the other part.

RECITALS

a. MGI carries on business as a pharmaceutical company and. in particular for the purpose of this Agreement, has entered into a License Agreement (as hereinafter defined) with Helsinn Healthcare SA, Via Pian Scairolo, 6912, Pazzallo, Switzerland (hereinafter called "HHC") by means of which MGI has been licensed with the right to distribute, promote, market and sell the Products (as hereinafter defined) in the Territory and has undertaken to purchase the Products exclusively from a source indicated or approved in writing by HHC.

b. HBP carries on business as a pharmaceutical manufacturer and trader and, in particular for the purpose of this Agreement, represents that it has been duly appointed by HHC as the supplier of the Products to MGI for the purpose of the sale of said Products by MGI.

c. The Parties agree that this preamble constitutes an integral part of this Agreement and all capitalized terms used in this preamble shall have the meaning as defined in Article 1 hereafter.

NOW, THEREFORE, in consideration of the foregoing and of the mutual covenants and conditions herein contained, the Parties hereby agree as follows:

ARTICLE 1- DEFINITIONS

The Following terms as used in this Agreement have, unless the context clearly indicates otherwise, the following meanings:

1.1 "Accounting Period" means the quarters ending 31st March, 30th June, 30th September and 31st December in each year throughout the term of this Agreement.

1.2 "Affiliate" means an organization that, whether now or in the future, controls. is controlled by or is under common control with a Party. For the purposes of this definition, the terms "controls," "controlled by," and "under common control with" as used with respect to any Party, means the possession (directly or indirectly) of fifty percent or more of the voting stock or other equity interest of a subject entity with the power to vote, or the power in fact to control the management decisions of such entity through the ownership of securities, by contract or otherwise.

1.3 "Compound" means the active pharmaceutical ingredient (3aS-2-[(S)-I-Azabicyclo[2.2.2]oct-3-yl]-2,3, 3a,4,5,6-hexahydro-l-oxo-IH-benzidelisoquinoline hydrochloride, having the genetic name palonosetron hydrochloride (INN) For use in human medicine.

1.4 "FDA" means the U.S. Food and Drug Administration or any successor agency.

1.5 "License Agreement" means the license agreement entered into between MGI and HHC on April 6th, 2001 granting MGI the exclusive right to distribute, market and sell the Products in the Territory.

1.6 "Net Sale Price" means the gross sale price in local currencies of the Products in the Territory by MGI and/or its Affiliates, including any local Affiliate in Canada, for arm's lenghth sales to any non-Affiliated third party less those normal and customary deductions made under Generally Accepted Accounting Principles to arrive at Product sales. Such deductions shall comprise any trade and quantity discounts, returns and allowances, rebates, cash discounts, sales and excise taxes, transportation and insurance charges, chargebacks and other amounts paid on sale or distribution of Product, provided that such deductions (i) are directly linked to and related to the gross sales invoiced amount, (ii) are specifically related to commercial policies having the purpose of acquiring, maintaining and maximising sales and enlarging the market share of the Product, (iii) do not exceed the average usual and customary deductions of this kind for similar products in the Field (as such term is defined in the Licence Agreement) in the Territory and (iv) shall not include any mark-up or other increase over costs actually incurred by MGI and/or its Affiliates in connection with such gross

sales. It is understood that said deductions shall not include any amount related to bad or doubtful debts. Where (a) a Product is sold as one of a number of items (bundled transaction) without a separate price; or (b) the consideration for the Product shall include any non-cash element; or (c) the Product shall be transferred in any manner other than an invoiced sale, the Net Sales applicable to the quantity of Product of any such transaction shall be deemed to be the average Net Sales for all other transactions of Product at that time in the Territory.

1.7 "Net Sales" means the gross sales in local currencies of all Products sold in the Territory by MGI and/or its Affiliates, including any local Affiliate in Canada, for arm's lenghth sales to any non-Affiliated third party less those normal and customary deductions made under Generally Accepted Accounting Principles to arrive at Product sales. Such deductions shall comprise any trade and quantity discounts, returns and allowances, rebates, cash discounts, sales and excise taxes, transportation and insurance charges, chargebacks and other amounts paid on sale or distribution of Product, provided that such deductions (i) are directly linked to and related to the gross sales invoiced amount, (ii) are specifically related to commercial policies having the purpose of acquiring, maintaining and maximising sales and enlarging the market share of the Product, (iii) do not exceed the average usual and customary deductions of this kind for similar products in the Field (as such term is defined in the Licence Agreement) in the Territory and (iv) shall not include any mark-up or other increase over costs actually incurred by MGI and/or its Affiliates in connection with such gross sales. It is understood that said deductions shall not include any amount related to bad or doubtful debts.

Where (a) a Product is sold as one of a number of items (bundled transaction) without a separate price; or (b) the consideration for the Product shall include any non-cash element; or (c) the Product shall be transferred in any manner other than an invoiced sale, the Net Sales applicable to the quantity of Product of any such transaction shall be deemed to be the average Net Sales for all other transactions of Product at that time in the Territory.

1.8 "Parties" means HBP and MGI and "Party" means either of them as the context indicates.

1.9 "Products" means the pharmaceutical preparations for human use in I.V. dosage form, containing the Compound as an active ingredient, in the formulation which will he described in the Registration. The current formulation as submitted to the Food and Drug Administration of the United States of America in the IND 39,797 Amendment # 64 and to the Therapeutic Products Programme of Canada in the IND 9427-H0836-21C is described in the First Appendix hereto.

1.10 "Registration" means any official approval, or authorization by the competent regulatory authorities, which is legally required to lawfully market the Products in the Territory, including, without limitation, any governmental price approval or reimbursement approved under a national health insurance system.

1.11 "Syntex Agreement" means a license agreement between HHC and Syntex (U.S.A.) LLC dated 23rd June 1998 by means of which HHC in-licensed world-wide rights on the Compound and Products.

1.12 "Territory" means the United States of America and its possessions arid territories (Puerto

Rico, United States Virgin Islands), and Canada and as provinces, possessions and territories.

ARTICLE 2 - PURCHASE OF PRODUCTS

2.1 Throughout the Term of this Agreement, and subject to the terms and conditions contained herein, MGI undertakes to purchase exclusively from HBP, and HBP undertakes to sell to MGI, MGI's entire requirements of the Products to be distributed, promoted, marketed and sold by MGI or MGI's Affiliates under the License Agreement.

2.2 MGI shall not use the Products for any other purpose than distributing, promoting, marketing and selling said Products in accordance with the terms and conditions of the License Agreement.

ARTICLE 3 - PRICE AND TERMS OF PAYMENT

3.1 The price of the Products purchased by MGI hereunder is as set forth in the Second Appendix hereto. At the fifth and at any following anniversary of the launch of the Product in the United States of America by MGI, the minimum supply price of the Products as indicated in the Second Appendix hereto shall be revised in accordance with the total percentage change in the price of pharmaceuticals products as reflected in the Pharmaceutical Price Index over the twelve month period preceding each said anniversary date.

3.2 Any payment by MGI for the delivered Products shall be effected by wire transfer of immediately available funds to an account designated in writing by HBP in United States Dollars within 30 (thirty) days from the date of receipt of the invoice (which shall be deemed to have been received on the date following the date of delivery to MGI by telefax) and be deemed paid

when freely received. MGI shall bear all costs in connection with effecting payments.

3.3 MGI shall in no case be entitled to off set or otherwise withhold any payment due to HBP in view of possible, justified or unjustified, claims against HBP.

3.4 In the event that, at any time throughout the term of this Agreement, MGI fails to pay for the supply of Products in accordance with the terms and conditions contained herein, and without prejudice to HBP's right to terminate this Agreement as per article 12.1 hereunder, MGI shall, at HBP's request, cause to be delivered to HBP a confirmed letter of credit from a primary international bank on terms and conditions reasonably satisfactory to HBP securing the payment obligations from MGI to HBP under this Agreement in connection with the following order of Products (the "Letter of Credit"). The Letter of Credit shall be irrevocable without the prior written consent of HBP. In the absence of such Letter of Credit, HBP shall be relieved from its obligation to supply the Products to MGI hereunder.

ARTICLE 4 - FORECASTS, ORDERS AND TERMS OF DELIVERY

4.1 MGI shall, prior to September 30th in each year throughout the term of this Agreement, supply HBP in writing with a purchase forecast for the Products for each Accounting Period of the following calendar year. Any such forecast shall be deemed to be a binding order by MGI for the first Accounting Period of such year. Moreover MGI shall issue its firm orders relevant to the three following Accounting Periods at least 90 (ninety) days in advance of the requested delivery date and, at each rime, it shall supply HBP

with its purchase forecast relevant to a further calendar year so as to maintain at all times a rolling twelve-month purchase forecast and shall promptly notify HBP of any projected changes thereto.

4.2 The Products will be supplied to MGI only against MGI's written order and all orders shall be subject to written acceptance and confirmation by HBP before becoming binding. Such acceptance and confirmation may be by facsimile or otherwise. Each order by MGI shall be for a minimum quantity corresponding to the sire of one production hatch of Products, as shall be indicated in due time by HBP, or multiples thereof.

HBP shall use commercially reasonable efforts to execute all orders received and accepted pursuant to this Article within 90 (ninety) days from the date of receipt of the relevant order by HBP. MGI's firm orders shall be at least 80% (eighty percent) and not more than 120% (one hundred and twenty percent) of its forecast of Products for the applicable Accounting Period as per Article 4.1 hereabove. HBP shall not be obliged to supply more than 100% (one hundred percent) of MGI's initial forecast of Products within the applicable Accounting Period. However, in the event that, in any Accounting Period, MGI's orders are more than 100% (one hundred percent) of the relevant forecasts. HBP agrees to use commercially reasonable efforts to supply MGI with amounts in excess of MGI's forecast of Product during said Accounting Period, on condition however that this shall not hamper, delay or otherwise prejudice supplies of Products to any other of HBP's customers. MGI shall keep throughout the term of this Agreement a stock of Products adequate to meet market demand and to cover possible shortages in the supplies of Products, such stock to

approximately correspond at least to three-month average sales. In turn, HBP undertakes to keep throughout the term of this Agreement a stock of Products in semi-finished form (i.e. vials without final packaging) approximately corresponding to at least to two-month average sales.

4.3 Any purchase order or acknowledgement thereof, whether printed, stamped, typed or written, shall be governed by the terms and conditions of this Agreement and none of the provisions of such purchase order or acknowledgement thereof shall he applicable, except those specifying quantity ordered, delivery dates and invoice information, and with respect to those specifications only to the extent that they are in compliance with the terms and conditions of this Agreement. To the extent there is any discrepancy between this Agreement and any purchase order or acknowledgement thereof, this Agreement will control.

4.4 All orders of Products shall be delivered DDU (Incoterms 2000) MGI's or MGI nominees warehouse in the United States of America. unless otherwise agreed in writing by the Parties. MGI shall be solely responsible for all customs clearance of, and import/export regulations for, the Products and it shall hear and pay all taxes, duties, levies and other charges imposed by reason of its purchase, import and resale of the Products.

4.5 If, for any reason, HBP is unable to supply MGI's firm orders for the Products up to the forecasted level, or is unable to supply such quantities in a manner meeting the Specifications, during any ninety (90) day period, the Parties shall promptly meet to discuss the reasons for such failure to supply, and HBP shall thereafter designate a third party

manufacturer to manufacture the Products. HBP shall provide to such third party manufacturer, appropriate manufacturing licenses and reasonable technical assistance to enable it to manufacture the Products, in a manner that minimizes disruption to MGI of Product supply.

ARTICLE 5 - QUALITY

5.1 HBP shall manufacture, or shall cause the Products to be manufactured, in accordance with applicable current Good Manufacturing Practice and with applicable specifications.

5.2 Each batch of Products shall be delivered to MGI accompanied by appropriate certificates of analysis, attesting the compliance of each relevant batch with the specifications for said Products as the same are contained in the Registration of the Products. MGI shall carry out appropriate visual inspection of the Products, as well as any other analysis which MGI may deem appropriate or necessary, upon receipt. Should it occur that any batch of Products does not meet said approved specifications, MGI shall, as soon as possible and in any case within 30 (thirty) days after receipt of the Products, give notice in wilting to HBP specifying in detail the claimed non-conforming characteristics of the Products. In the absence of MGI's notification within the said term, MGI shall be deemed to have accepted such Products. Should HBP recognize that such Products delivered to MGI do not meet the approved specifications, and provided MGI demonstrates that the Products have been properly handled and stored after delivery, HBP shall replace, at its own cost, such Products. Such replacement shall be done, to the extent possible, in accordance with the timing reasonably agreed among the Parties which, in any

event, shall be as soon as reasonably possible thereafter. It is understood and agreed that HBP's total responsibilities hereunder shall he limited to said replacement of Products. Should HBP not he in agreement with MGI's claim of defect, a sample of the alleged defective Products shall be submitted for analysis to an independent laboratory to be agreed in good faith between MGI and HBP in writing. The decision of such laboratory shall be final and binding for both MGI and HBP and the corresponding expenses will be paid by the Party found to be in error.

5.3 HBP shall at any time be free to determine the manufacturer and the place of manufacture of the Products, subject however to applicable laws and regulations and to compliance with the License Agreement. In no event shall MGI be entitled to manufacture any Products by virtue of this Agreement.

5.4 MGI shall store and distribute, and shall cause the Products to be stored and distributed, according to applicable current Good Manufacturing Practice or any other applicable laws and regulations. MGI shall permit HBP's representatives, during normal business hours and upon three business days advance notice in writing hut not more than once a year or as otherwise reasonably requested by HBP, to inspect those areas of the warehouses of MGI, its Affiliates and its distributors where the Products are inspected, analyzed or stored, for the purpose of verifying compliance with applicable laws and regulations as well as with this Agreement. Such inspection shall include, without limitation, the right to examine any relevant internal procedures or records of MGI, its Affiliates and distributors. MGI shall give and shall cause its Affiliates and distributors to give, all

necessary assistance for a full and correct carrying out of the inspection by HBP. No such inspection by HBP shall relieve MGI, its Affiliates and distributors of any of their obligations under this Agreement in any way whatsoever.

5.5 The Products shall be supplied by HBP or HBP's nominee to MGI in a secondary package inclusive of leaflet, ready for distribution. Artwork and all necessary films for printing packs, package inserts, leaflets and labels will be prepared and supplied by MGI, at its expenses, based upon indications, box design and measurements provided by HBP. Any change shall have to be communicated by MGI to HBP at least 6 (six) months in advance of its enforcement. The costs relevant to the change, including costs relevant to repackaging or disposal of Products in stock at HBP, (i) shall be entirely borne by MGI if the change has been requested by MGI, and (ii) shall be shared between the parties in case the change is required by any regulatory authority or is jointly deemed advisable by the Parties.

5.6 Events concerning Product recall, complaint, field alert or Product withdrawal relevant to the Products marketed by MGI in the Territory shall be governed by the procedures and rules established in the Licence Agreement.

ARTICLE 6 - RECORDS AND REPORTS

6.1 MGI shall submit to HBP at the end of each Accounting Period a written statement signed by a responsible officer of MGI which shall show the units of Products sold or otherwise disposed of by MGI, the gross sale price and the Net Sale Price of the Products and any change thereof, together with a detailed listing and appropriate evidence of any and all

discounts granted for each client, wholesaler and/or distributor as necessary to permit to HBP to calculate and verify the supply price of the Products as per the Second Appendix hereto, the gross sales and the Net Sales for said Accounting Period and the existing stock of Products in MGI's, its Affiliates' and its distributors' warehouses. Throughout the term of this Agreement and for a period of at least 3 (three) years thereafter, MGI shall keep complete and accurate hooks. records and accounts in accordance with sound accounting practice covering all its operations hereunder as necessary to determine and verify the units of Products sold or otherwise disposed of by MGI, the Net Sale Price of the Products, the Net Sales for each Accounting Period, and any change thereof. HBP shall have the right, at any time throughout the term of this Agreement and for a period of three years thereafter, during normal business hours and upon at least three (3) business days advance notice, to have such books, records and accounts inspected and audited by its duly authorized representatives or, at HBP's discretion, by an independent certified public accountant to be nominated by HBP and reasonably acceptable to MGI. MGI shall fully co-operate with HBP, its authorized representatives or independent certified public accountant and make available all work papers and other information reasonably requested in connection herewith. In the event the inspection or audit reveals that an underpayment has occurred, MGI shall immediately pay to HBP any underpaid amount within 10 (ten) days of the date HBP delivers to MGI the relevant inspection or audit report. In case of an underpayment of at least five percent (5%) of the amounts owing during the audited period, MGI shall also bear all the costs of the inspection or audit and any overdue amounts hereunder shall bear interest at

the prime rate applicable in Switzerland as of the date such payment was originally due.

6.2 Each of the Parties hereby agrees that any and all communications sent to or received from the other Parry hereunder, including but not limited to those described at Article 13.2 hereunder, shall he immediately sent in copy by telefax to HHC.

ARTICLE 7- REPRESENTATIONS AND WARRANTIES

7.1 HOP hereby represents and warrants to MGI as follows:

7.1.1 HBP has beets duly organized and is validly existing as a corporation in good standing under the laws of the Republic of Ireland. HBP has the corporate power and authority to enter into this Agreement and to consummate the transactions contemplated by this Agreement.

7.1.2 The execution, delivery and performance of this Agreement, and the consummation of the transactions contemplated by this Agreement, by HBP have been duly and validly authorized by all requisite corporate actions. This Agreement constitutes a legal, valid and binding agreement of HBP enforceable against HBP in accordance with its terms.

7.1.3 The execution, delivery and performance by HBP of this Agreement requires no action by or in respect of, or consent or approval of, or filing with, any Governmental Authority.

7.1.4 The execution, delivery and performance by HBP of the contemplated transactions do not and will not (A) contravene or conflict with the charter or bylaws or HBP, as applicable, (B) contravene or conflict with or constitute a violation of any provisions

of any applicable law binding upon HBP, or (C) constitute a default in any material respect under or give rise to any right of termination, cancellation or acceleration of, any agreement or instrument to which HBP is a party, or to a loss of any material benefit to which HBP is entitled.

7.1.5 There is no action, suit, investigation or proceeding pending against, or to the knowledge of HBP, threatened against or affecting, HBP before any court, arbitrator or any governmental authority, including but not limited to Regulatory Authorities, that in any manner challenges or seeks to prevent, enjoin, alter or materially delay the contemplated transactions, and, to the knowledge of HBP, there is no reasonably valid basis for any such action, suit, investigation or proceeding to be brought.

7.1.6 The persons executing this Agreement on behalf of HBP are duly authorized to do so and by so doing have bound HBP to the terms and conditions of this Agreement.

7.1.7 HBP has been duly authorized and entrusted by HHC to supply the Products to MGI.

7.2 MGI hereby represents and warrants to HBP as follows:

7.2.1 MGI is a corporation duly incorporated, validly existing and in good standing under the laws of the state of its incorporation and has all corporate powers and all governmental licenses, authorizations, consents and approvals required to carry on its business as now conducted and as contemplated to be conducted in connection with the transactions contemplated by this Agreement (the "Contemplated Transactions"). MGI is duly qualified to do business as a foreign corporation in each jurisdiction where the

character of the property owned or leased by it or the nature of its activities (after giving effect to the Contemplated Transactions) make such qualification necessary to carry on its business, except where the failure to so qualify would not have a material adverse effect on MGI.

7.2.2 The execution, delivery and performance by MGI of this Agreement and the consummation by MGI of the Contemplated Transactions are within the corporate powers of MGI, and have been duly authorized by all necessary corporate action on the part of MGI. This Agreement constitutes a legal, valid and binding agreement of MGI, enforceable against MGI as applicable in accordance with its terms.

7.2.3 The execution, delivery and performance by MGI of this Agreement requires no action by or in respect of, or consent or approval of. or filing with, any Governmental Authority, other than filings with the SEC in fulfillment of MGI's disclosure obligations under U.S. securities laws.

7.2.4 The execution, delivery and performance by MGI of the Contemplated Transactions do not and will not (A) contravene or conflict with the charter or bylaws of MGI, as applicable, (B) contravene or conflict with or constitute a violation of any provisions of any Applicable Law binding upon MGI, or (C) constitute a default in any material respect under or give rise to any right of termination, cancellation or acceleration of, any agreement or instrument to which MGI is a party, or to a loss of any material benefit to which MGI is entitled.

7.2.5 There is no action, suit, investigation or proceeding pending against, or to the knowledge of MGI, threatened against or affecting, MGI before any

court, arbitrator or any governmental authority, including but not limited to regulatory authorities, that in any manner challenges or seeks to prevent, enjoin, alter or materially delay the Contemplated Transactions, and, to the knowledge of MGI, there is no reasonably valid basis for any such action, suit investigation or proceeding to he brought.

7.2.6 The persons executing this Agreement on behalf of MGI are duly authorized to do so and by so doing have bound MGI to the terms and conditions of this Agreement.

ARTICLE 8 - LIABILITIES, INDEMNITIES AND INSURANCE

8.1 MGI shall be fully liable for and shall defend, indemnify and hold HBP and its Affiliates, officers, directors and employees wholly free and harmless from and against any and all liabilities, damages, losses, costs, taxes, expenses (including reasonable attorneys' fees and other expenses of litigation and arbitration), claims, demands, suits, penalties, judgements or administrative and judicial orders arising out of or resulting front any claim, suit or proceeding to the extent arising out of or resulting from (a) any failure by MGI, its local distributors or Affiliates to comply with any applicable laws, regulations and/or administrative decision regarding the Products; (b) the storage. distribution, sampling, record-keeping, analysis, transfer or sale of the Products; (c) the promotion, advertising and marketing of the Products; (d) the failure of any Products supplied hereunder to comply with the applicable approved specifications that (i) could have been detected by MGI carrying out visual inspection on the supplied Products with ordinary diligence or (ii) results from any Products which have been altered, changed, packed or re-

packed, processed or otherwise treated other than in strict accordance with HBP's instructions and specifications; or (e) any negligent or wrongful act or omission and/or any breach by MGI or by any of its local distributors and/or Affiliates of any of MGI's obligations, representations and/or warranties hereunder.

8.2 HBP shall be liable for and shall defend, indemnify and hold MGI and its Affiliates, officers, directors and employees free and harmless from and against any and all liabilities, damages, losses, costs, expenses (including reasonable attorneys' fees and other expenses of litigation and arbitration), claims, demands, suits, penalties, judgments or administrative and judicial orders, arising out of or in any way resulting from any claim, suit or proceeding to the extent arising out of or resulting from (a) failure of any Products supplied hereunder to conform to the applicable approved specifications, excluding however any liabilities, losses, damages, costs, expenses claims, demands, suits, penalties, judgments or orders resulting from any such non-compliance that (i) could have been detected by MGI carrying out visual inspections on the supplied Products with ordinary diligence or (ii) results from any Products which have been altered, changed, packed or re-packed, processed or otherwise treated other than in strict accordance with HBP's instructions and specifications; or (b) any negligent or wrongful act or omission and/or breach by HBP of any of its obligations and/or warranties hereunder.

8.3 Being understood that each of the Parties hereto shall take all reasonable steps to avoid or mitigate any loss, damage or liability which might give rise to a claim under this Agreement, a Party seeking

indemnification pursuant to this Article 8 (an "Indemnified Party") shall give prompt and full written notice to the Party from whom such indemnification is sought (the "Indemnifying Party") of the assertion of any claim, or the commencement of any action, suit or proceeding in respect of which indemnity is or may he sought hereunder, provided however that no failure to give such notice or co-operation shall relieve the Indemnifying Party of any liability and/or obligation hereunder (except to the extent the Indemnifying Party has suffered actual prejudice thereby). Subject to any right of Syntex (U.S.A.) LLC under the Syntex Agreement, the Indemnifying Party shall have the sole right to control the defense and settlement thereof. The Indemnified Party will give the Indemnifying Party such information with respect thereto as the Indemnifying Party may reasonably request and will co-operate with the Indemnifying Patty in the defense of said claim, suit or proceeding as the Indemnifying Party may reasonably request. The Indemnified Patty shall not, except at its own cost, voluntarily make any payment or incur any expense with respect to any claim, suit or proceeding without the prior written consent of the Indemnifying Party. In addition, the Indemnifying Party shall be subrogated to the rights of the Indemnified Party against any third party, and such Indemnified Party hereby assigns to the Indemnifying Party all claims, causes of action and other rights which the Indemnified Party may then have against any third party, including Affiliates and, in the case of HBP, against any contract manufacturer of the Products, with respect to the claim, suit or proceeding which is the subject of the claim for indemnification hereunder. Conversely, and without in any way limiting the obligation of either Party to indemnify the other Party

as herein provided, to the extent that either Party shall fail to perform its indemnification obligations under this Article 8, such Party owing a duty of indemnification hereby assigns to the other Party all claims, cause of action and other rights which the Party owing such duty may then have against any third party, including Affiliates and, in the case of HBP, against any contract manufacturer of the Products, with respect to the claim, suit or proceeding.

8.4 MGI shall be solely responsible towards its customers for handling all matters concerning the Products, subject to cooperation with HBP on any recall or other matters that may be injurious to HBP. MGI shall be responsible for any expired Products, whether stored by MGI and/or its local distributors or returned by wholesalers, pharmacists, doctors, hospitals to whom said Products have been sold. HBP shall (i) reimburse to MGI documented reasonable costs incurred by MGI with regard to the destruction of expired Products, up to a maximum quantity of 1% (one percent) of the units of Products sold by MGI in any calendar year and (ii) replace free of charge said expired Products, up to a maximum quantity of 1% (one percent) of the units of Products sold by MGI in any calendar year. Except as provided hereabove, MGI shall not be entitled to any replacement of Products nor to any compensation of any kind from HBP in connection herewith. MGI shall indemnify, defend and hold HBP and its Affiliates, directors, officers and employees wholly free and harmless from and against any and all liabilities, damages, losses, costs, expenses (including reasonable attorneys' fees and other expenses of litigation and arbitration), claims, demands, suits, penalties, judgments or administrative and judicial orders arising therefrom; except with respect to any recall or other regulatory action arising

from any breach by HBP or its Affiliates of any warranty, representation or other material obligation contained in this Agreement or the negligence or willful misconduct of HBP or its Affiliates.

8.5 Each Party shall indemnify and hold the other Party wholly harmless from and against any and all liabilities, damages, losses, costs, expenses (including reasonable attorneys' fees and other expenses of litigation and arbitration), claims, demands, suits, penalties, judgments or administrative and judicial orders arising out of any behavior contrary or in excess to the provisions of Article 13.1 hereunder.

8.6 THE SOLE REPRESENTATIONS AND WARRANTIES THAT HBP MAKES WITH RESPECT TO THE MATTER CONTEMPLATED BY THIS AGREEMENT ARE EXPRESSLY SET FORTH IN ARTICLE 7.1. WITHOUT LIMITING THE GENERALITY OF THE FOREGOING, HBP MAKES NO REPRESENTATION OR WARRANTY OF ANY KIND, EXPRESS OR IMPLIED, OF MARKETABILITY, CAPACITY OR FITNESS FOR A PARTICULAR PURPOSE WITH RESPECT TO THE PRODUCTS. NO ORAL OR WRITTEN REPRESENTATION BY OR ON BEHALF OF HBP SHALL BE INTERPRETED TO CONTAIN ANY SUCH WARRANTY. NEITHER MGI NOR ANY OF ITS EMPLOYEES OR REPRESENTATIVES IS AUTHORISED TO GIVE ANY WARRANTIES OR MAKE ANY REPRESENTATION ON BEHALF OF HBP.

8.7 THE SOLE REPRESENTATIONS AND WARRANTIES THAT MGI MAKES WITH RESPECT TO THE MATTER CONTEMPLATED BY THIS AGREEMENT ARE EXPRESSLY SET FORTH IN ARTICLE 7.2. AND MGI HEREBY DISCLAIMS ALL OTHER REPRESENTATIONS OR WARRANTIES

OF ANY KIND, EXPRESS OR IMPLIED. NO ORAL OR WRITTEN REPRESENTATION BY OR ON BEHALF OF MGI SHALL BE INTERPRETED TO CONTAIN ANY SUCH WARRANTY. NEITHER HBP NOR ANY OF ITS EMPLOYEES OR REPRESENTATIVES IS AUTHORISED TO GIVE ANY WARRANTIES OR MAKE ANY REPRESENTATION ON BEHALF OF MGI.

8.8 NOTWITHSTANDING ANY OTHER PROVISION OF THIS AGREEMENT, NEITHER OF THE PARTIES SHALL BE LIABLE TOWARDS THE OTHER FOR INDIRECT, SPECIAL, PUNITIVE EXEMPLARY, INCIDENTAL OR CONSEQUENTIAL DAMAGES, INCLUDING WITHOUT LIMITATION LOSS OF PROFITS OR REVENUES. REGARDLESS OF WHETHER SUCH DAMAGES WERE FORESEEABLE OR NOT. THIS CLAUSE WILL HOWEVER NOT BE APPLICABLE IN CASE OF BREACH BY MGI OF THE PURCHASE OBLIGATIONS STATED AT ARTICLE 2 AND BREACH BY EITHER PARTY OF THE CONFIDENTIALITY AND NON-USE OBLIGATIONS STATED AT ARTICLE 9 OF THIS AGREEMENT.

of this Agreement on all policies of general commercial liability insurance and product liability insurance covering MGI, which coverage shall, when MGI either initiates clinical trials on the Products or begins marketing or distributing the Products for commercial sale or for promotional purposes, have limits of liability which are commercially reasonable in the Territory but shall he not less than USD 30,000,000 (United States Dollars thirty million) per loss occurrence. Within 5 (five) days of the Effective Date and of each beginning of each policy period, MGI shall provide HBP with a certificate evidencing the coverage

required hereby and the amount thereof. Such coverage shall be with a reputable insurance company having at least an A.M. Best "A" rating and shall have to be maintained for not less than 6 (six) years following expiration or termination of this Agreement for any reason or if such coverage is of the "claims made" type, for ten years following expiration or termination of this Agreement for any reason.

ARTICLE 9 - CONFIDENTIALITY

9.1 MGI shall treat as strictly confidential, and shall use solely for the purpose of and in accordance with this Agreement, any and all information, data and/or document received hereunder or in connection with the Contemplated Transaction not generally known to the trade (all hereinafter referred to as the "Confidential Information"). MGI shall not make such Confidential Information available to any third Party, including any of its Affiliates, except to competent government agencies to which it will be necessary to disclose such Information, and in this case (a) strictly to the extent requested by said agencies and (b) only upon exercise of its best efforts to cause said agencies to maintain confidentiality thereof.

9.2 Such Confidential information shall only he made available to such employees of MGI who are directly and necessarily involved in the authorized use of Confidential information and who are subject to a secrecy obligation by contract, to the extent strictly necessary to perform their duties and obligations hereunder.

9.3 Notwithstanding expiration or termination of this Agreement for any reason, these confidentiality and non-use obligations shall continue until the Confidential Information has become generally known

to the public, provided however that nothing contained herein shall in any way restrict or impair the right of MGI to use, disclose or otherwise deal with Information which MGI can demonstrate to HBP by clearly convincing documentation.

9.3.1 is or hereafter becomes part of the public domain through no act or omission of MGI, its employees, Affiliates and/or local distributors, or

9.3.2 MGI was in lawful possession of prior to receipt of the Confidential Information from HBP, or

9.3.3 previously was, or at any time hereafter is, received in good faith by MGI from sources other than HBP and/or HHC and which did not originate, directly or indirectly, from Syntex. or

9.3.4 at the time of disclosure, was known by MGI or an Affiliate or local distributor, or after disclosure was independently developed by MGI, an Affiliate or local distributor without use of the Confidential Information.

9.4 HBP shall keep strictly confidential, in the same way mutatis mutandis as provided here above for MGI in respect of Confidential Information, any MGI Confidential Information (as defined herein) received from MGI hereunder, except as otherwise specifically provided in this Agreement. As used herein, the term "Confidential Information" shall mean all information disclosed by MGI to HBP relating to the markets, customers, suppliers, patents or patent applications, inventions, know-how, data or information, products, research and development, procedures, designs, formulas, business plans, financial projections, employees, consultants or any other similar aspects MGI's present or future business, whether such

information is disclosed in written, oral, electronic, graphic or other format.

ARTICLE 10 - FORCE MAJEURE

10.1 Except as set forth in Section 4.5, if the performance of this Agreement is prevented or restricted by government action, war, fire, explosion, flood, strike, lockout, embargo, act of God, or any other similar cause beyond the control of the defaulting Party, the Party so affected shall be released for the duration of the force majeure, or such other period agreed between the Parties as being reasonable in all circumstances, from its contractual obligations directly affected by the force majeure, provided that the Party concerned shall:

10.1.1 give prompt notice in writing to the other Party of the cause of force majeure;

10.1.2 use all best endeavors to avoid or remove such cause of non-performance:

10.1.3 continue the full performance of this Agreement as soon as such cause is removed.

10.2 The Parties shall take all reasonable steps to minimize the effects of force majeure on the performance of this Agreement and shall, if necessary, agree on appropriate measures to be taken. Should the force majeure continue for more than 6 (six) months, then the other Party shall have the right to terminate this Agreement forthwith.

10.3 Notwithstanding anything contained in this Article 10, obligations to pay money accruing prior to the force majeure event are never excused by force majeure.

ARTICLE 11 - TERM

11.1 This Agreement comes into force at the Effective Date hereof. Unless terminated earlier pursuant to the provisions hereof, it shall terminate automatically at termination or expiration for any reason of the License Agreement.

ARTICLE 12 - TERMINATION

12.1 Each of the Parties reserves the right to terminate this Agreement in case of any substantial or persistent breach of any of the terms and conditions of this Agreement by the other Party. The defaulting Party shall be given in writing a 60 (sixty)-day period, except as otherwise specifically provided, to fulfill its obligations hereunder and, if after such period it is still in breach of the Agreement, the other Party shall have the right to terminate this Agreement by written notice to the defaulting Party. In the event of a breach by MOI of any of the terms and conditions of this Agreement entitling HBP to terminate this Agreement under this Article 12.1, HBP shall immediately and fully inform HHC in writing for appropriate actions by HHC. In particular, MOI hereby acknowledges and agrees that termination of this Agreement by HBP pursuant to this Article 12.1 shall entitle HHC to terminate the License Agreement.

12.2 Either Party shall have the right to terminate this Agreement upon written notice to the other Party, if such other Party shall become insolvent or shall make an assignment for the benefit of creditors or become involved in receivership, bankruptcy or other insolvency or debtor relief proceedings, or any similar proceedings, or in proceedings. voluntary or forced, whereby the Party involved is limited in the free and

unrestrained exercise of its own judgment as to the carrying out of the terms of this Agreement.

12.3 HBP shall have the right to terminate this Agreement by written notice to MOI if MOI infringes the confidentiality and/or non-use obligations provided for in Article 9 hereabove. MOI shall have the right to terminate this agreement by written notice to HBP if HBP breaches the confidentiality and/or non-use obligations provided for in Article 9.4 hereabove.

12.4 Without limiting the generality of the foregoing, termination or expiration of this Agreement for any reason shall not extinguish any existing claims either of the Parties may have for indemnification and shall not preclude either of the Parties from pursuing any claim for indemnification such Party otherwise may have to the extent that the circumstances giving rise to such claim arose prior to, on or after the date of termination or expiration.

12.5 Upon expiration or termination of this Agreement for any reason, MOI shall promptly terminate using any and all information and data received hereunder and return or deliver all such materials to HBP without retaining copies, notes, summaries or translations thereof.

12.6 Unless otherwise set forth herein, the Parties' remedies under this Agreement are intended to he cumulative and not mutually exclusive.

ARTICLE 13 - MISCELLANEOUS

13.1 Independent contractor status

The status of HBP and MGI under the business arrangement established by this Agreement is that of independent contractors. MGI shall perform as an independent contractor in relation to both HBP and

MGIs customers and, accordingly, MGI shall purchase the Products from HBP or HBP's nominee and resell them to its customers in its own name and for its own account. MGI has no authority whatsoever to act as an agent or representative of HBP nor any authority or power to contract in the name of or create any liability against or otherwise bind HBP in any way for any purpose, nor shall HBP have such authority or power to so bind MGI.

13.2 Notices

All reports, notices and communications given or made pursuant to this Agreement by one Party to the other shall be validly given or made for all purposes, in the absence of acknowledgement of receipt, on the date of mailing if mailed by registered airmail or by international courier to the addressee Party at the following addresses, respectively:

HELSINN BIREX PHARMACEUTICALS LTD.
Damastown
Mulhuddart
Dublin 15
Republic of Ireland
For the attention of: General Manager

With copy to:
HELSINN HEALTHCARE SA
P.O. B0X 357
6915 Pambio-Noranco
SWITZERLAND
For the attention of Legal Department

MGI PHARMA INC.
6300 West Old Shakopee Road
Suite 110
Bloomington
MN 55435-2318. USA

For the attention of: Manager, Legal Affairs

With copy to:
Dorsey & Whitney LIP
220 South Sixth Street
Minneapolis, MN 55402
For the attention of: Timothy S. Hearn

13.3 Binding Effect

Subject to the provisions of article 13.6 herein, this Agreement shall inure to the benefit of, and be binding upon, the respective successors of the Parties.

13.4 Waiver

The failure of a Party to insist upon strict performance of any of the terms and conditions of this Agreement by the other Party shall not constitute a waiver of any of the provisions hereof and no waiver by a Party of any of said term and conditions shall be deemed to have been made unless expressed in writing and signed by such waiving Party.

13.5 Interpretation

13.5.1 The language of this Agreement is English. No translation into any other language shall be taken into account in the interpretation of the Agreement itself.

13.5.2 The headings in this Agreement are inserted for convenience only and shall not affect its construction.

13.5.3 Where appropriate, the terms defined in Article 1 hereabove and denoting a singular number only shall include the plural and vice versa.

13.5.4 References to any law, regulation, statute or statutory provision includes a reference to the law,

regulation, stature or statutory provision as from time to time amended. extended or re-enacted.

13.6 Assignment

This Agreement cannot be transferred. sublicensed, assigned or otherwise disposed of (by operation of law or otherwise) by MOI without the prior, written authorization of HBP, which authorization shall not be unreasonably withheld, provided however that MOI shall he entitled to assign this Agreement in conjunction with the assignment of the License Agreement in accordance with the terms and conditions thereof. HBP shall have the right to assign or transfer, in whole or in part, this Agreement to any of its Affiliates

13.7 Statements to the Public

Neither HBP nor MOI shall make or procure or permit the making of any announcement or statement to the public with respect to this Agreement, its subject matter or any ancillary matter without the prior consent of the other Party, which consent shall not be unreasonably withheld.

The wording and the timing of any press release or of any other announcement and/or statement to the public shall have to be agreed upon in advance between the Parties.

Nothing herein shall prohibit MOI from disclosing information to the extent required by the U.S. Securities and Exchange Commission, Nasdaq or other similar authorities. It is however understood and agreed that (a) the contents of any copy of this Agreement, or of tiny other agreement between the Parties, which has to be sent to the SEC shall have to be previously agreed upon between the Parties and shall be in redacted form to maintain the

confidentiality of proprietary and/or competitivity sensitive information, and (b) MOI shall use its best efforts to obtain authorization by the SEC to keep confidential any information which is deemed to be confidential by the Parties or any of them or which may, in either Party's opinion, put a competitive advantage to third parties.

13.8 Expenses

Unless specifically and expressly provided for to the contrary in this Agreement, each of the Parties shall hear its own expenses incurred in connection with the performance of this Agreement.

13.9 Survival

The following provisions shall survive expiration or termination of this Agreement for any reason: Articles 1 (whole clause), 6 (whole clause), 8 (whole clause), 9 (whole clause), 12.4 through 12.6, 13 (whole clause), 15 (whole clause) and 16 (whole clause).

ARTICLE 14 - APPENDICES

14.1 The following Appendices shall he an integral part of this Agreement:

Appendix I: Products

Appendix 2: Price

ARTICLE 15 - LAW TO GOVERN AND ARBITRATION

15.1 This Agreement shall be governed by and construed in accordance with the law of Switzerland.

15.2 It is the express decision of the Parties that any dispute which may arise between the Parties concerning this Agreement, which cannot be settled amicably, shall be submitted to arbitration for final

decision. Also, any dispute as to the applicability of the arbitration clause shall be subject to arbitration. Notwithstanding the above, each Party expressly reserves the right to seek judicial relief from a court of competent jurisdiction if the other Party is or appears to be in violation of such other Party's obligations of non-use and non-disclosure under Article 9 above, including. without limitation, any injunction or other preliminary relief.

15.3 It is expressly agreed that arbitration shall be held in English language in Geneva (Switzerland) and conducted under the Rules of Arbitration of the International Chamber of Commerce. The court of arbitration shall consist of three arbitrators. Each Party is entitled to nominate one arbitrator. If. within one month after receipt of the request for arbitration filed by one Party, the other has not yet appointed an arbitrator, such arbitrator shall be appointed by the International Court of Arbitration of the International Chamber of Commerce on request of the first Party. The two arbitrators shall nominate the president of the court of arbitration, who shall be a lawyer qualified to practice and currently practicing as an attorney-at-law or as a judge. If they cannot come to terms within one month, the president of the court of arbitration shall be nominated by the International Court of Arbitration of the International Chamber of Commerce, on request of the more diligent Party.

15.4 If one of the arbitrators is unable to fulfil his/her duties for any reason the Party having nominated him/her shall nominate another arbitrator within one month, otherwise this arbitrator will be nominated by the International Court of Arbitration of the International Chamber of Commerce.

15.5 If the arbitrators or the president have to be replaced, the proceedings do not have to he started anew and will continue at the point where they were stopped.

15.6 The court of arbitration is hereby expressly instructed to act with most diligence and to keep any term as short as possible and to render the decision as soon as possible.

15.7 The Parties hereby stipulate that any arbitration hereunder shall be subject to the following rules: (a) the arbitrators may not award or assess punitive damages against either Party; and (b) each Party shall bear its own costs and expenses of the arbitration and one-half (1/2) of the fees and costs of the arbitrators, subject to the power of the arbitrators, in their sole discretion, to award all such reasonable costs, expenses and fees to the prevailing Party.

15.8 The Parties agree that the arbitrator's award shall be the sole and exclusive remedy between them regarding any claims, counter-claims, issues or accountings presented or pled to the arbitrator and that any costs, fees or taxes incident to enforcing the award shall be, to the maximum extent permitted by law, charged against the Party resisting such enforcement.

15.9 Notwithstanding the foregoing, any Party may bring a case of action against the other Party before any court of competent jurisdiction at the domicile of the defendant Party, if and to extent that any arbitral award rendered in the arbitration proceedings is unenforceable.

15.10 Subject to the provisions of Article 15.9, in the event that an award is rendered pursuant to this Article 15 by an arbitrator in favor of HBP, the Parties

acknowledge and agree that such award shall be enforceable by HBP, and MGI hereby consents to the exclusive jurisdiction for purposes of enforcement of any such award against MGI to the United States District Court for the District of Delaware, or, if jurisdiction or venue cannot he laid therein, the jurisdiction of any courts in the State of Delaware. Each of the Parties hereby consents to the exclusive jurisdiction of such courts (and of the appropriate appellate courts) for the purposes set forth above.

ARTICLE 16 - ENTIRETY OF AGREEMENT AND SEVERABILITY

16.1 This Agreement supersedes all prior agreements and understandings, whether oral or written, made by either Party or between the Parties and constitutes the entire Agreement of the Parties with regard to the subject matter hereof. The Parties however acknowledge and understand that (a) the existence and validity of this Agreement depend upon and are conditional upon the existence and validity of the License Agreement and (b) in case of any discrepancy between the License Agreement and this Agreement, this Agreement shall be construed in a manner consistent with the License Agreement. This Agreement shall not be considered extended, cancelled or amended in any respect unless done so in writing and signed on behalf of the Parties hereto.

16.2 The Parties hereby expressly state that it is the intention of neither Party to violate any rule, law and regulations. If any provision of this Agreement is rendered invalid or unenforceable, the Parties agree to renegotiate such provision in good faith and to replace it with valid and enforceable provisions in such a way as to reflect as nearly as possible the intent and purpose of the original provision,

IN WITNESS WHEREOF, the Parties hereto have caused this Agreement to be executed in duplicate by their duly authorized officers.

For and on behalf of
HELSINN BIREX PHARMACEUTICALS Ltd

/s/ Riccardo Braglia
Riccardo Braglia
Proxy

/s/ Enrico Braglia
Enrico Braglia
Proxy

For and on behalf of
MGI PHARMA, INC.

/s/ Charles N. Blitzer
Charles N. Blitzer
President and Chief
Executive Officer

/s/ Leon O. Moulder, Jr.
Leon O. Moulder, Jr.
Executive Vice President

FIRST APPENDIX

To an Agreement between HELSINN BIREX PHARMACEUTICALS LTD and MGI PHARMA, INC. dated April 6th, 2001

THE PRODUCTS

Qualitative description of the Products as submitted to the United States Food and Drug Administration under IND 39,797 Amendment # 64 and to the Therapeutic Products Programme in Canada under IND 9427-H0836-2IC

1. Palonosetron HCl Intravenous injection is supplied as a sterile, isotonic solution in 5 ml Type I clear glass vials each containing 5 ml of product. The product is clear and colorless solution, and contains the equivalent of either 0.05 mg/mL or 0.15 mg/mL of Palonosetron free base. The formulation also contains mannitol as a tonicifying agent, edetate disodium as a chelating agent and citrate buffer to maintain the pH of the solution at the target pH of 5 (±0.5).

2. The product is terminally sterilized.

SECOND APPENDIX

To an Agreement between HELSINN BIREX PHARMACEUTICALS LTD and MGI PHARMA, INC. dated April 6th, 2001

PRICE OF PRODUCTS

1. The Products will be supplied to MGI in finished packed form ready for marketing at a price corresponding to 29% (twenty-nine percent) of the Net Sale Price of said Products, provided however that, irrespective of the Net Sale Price of the Products, in no event said supply price for Products destined to the market of the United States of America shall be lower than USD $28.50 (United States Dollars twenty-eight and fifty cents) per vial in final package. An appropriate minimum supply price for Products destined to the market of Canada shall be discussed and established in good faith by the Parties in due time.

2. Within 31st May and 30th November in each calendar year throughout the term of this Agreement, MGI shall notify in writing HBP the Net Sale Price on which basis HBP shall calculate the supply price of the Products for the following six-month periods starting.

respectively, on 1st January and 15th July. Within 5 (five) days of the end of each Accounting Period, it shall be calculated the compensation for the supply of the Products so that it corresponds to 29% (twenty nine percent) of the Net Sales of said Accounting Period, provided however that sales by MGI of the 10% (ten percent) free goods which will he supplied in the First and in the second year from launch and of the 5% (five percent) free goods which will be supplied in the third year from launch in accordance with paragraph 3 hereunder, shall not be considered in the determination of Net Sales for the purpose of calculating the 29% compensation for the supply of Products. Resulting balances, if any, due to differences between the compensations to HBP calculated as above and the sum actually paid by MGI for the purchase of the Products, shall be liquidated between the Parties within 30 (thirty) days of the end of each calendar year.

3. The Parties further agree that HBP shall supply 10% (ten percent) free goods on top of the ordered quantities in the first and in the second year from launch, and 5% (five percent) free goods on top of the ordered quantities in the third year from launch.

HELSINN

April 10 2001

MGI PHARMA SIGNS EXCLUSIVE LICENSE AGREEMENT WITH HELSINN HEALTHCARE SA, FOR. PALONOSETRON, A PHASE 3 ANTI-EMETIC

MINNEAPOLIS end LUGANO, SWITZERLAND, April 10, 2001 – MGI PHARMA INC., (Nasdaq: MOGN) and HELSINN HEALTHCARE SA, a privately owned pharmaceutical group with headquarters in Switzer-land, today announced that they have signed the definitive agreement granting MGI PHARMA exclu-sive North American license and distribution rights to palonosetron. The signing of the letter of intent for this agreement was previously announced in February. Palonosetron is a potent and selective 5-HT, antago-nist with an extended half-life, in Phase 3 develop-ment for the prevention of chemotherapy-induced nausea and vomiting (CINV), Completion of the Phase 3 trials could allow for NDA (New Drug Application) submission in the first half of 2002. When launched, palonosetron will compete in the $1 billion North American CINV market.

"We are looking forward to entering the supportive care segment of oncology, the successful completion of the Phase 3 program and approve process for palonosetron, and the opportunity to demonstrate the role that this novel agent can have in preventing chernotherapy-induced nausea and vomiting for can-cer patients," commented Chuck Blitzer, president and CEO of MGI PHARMA. "Palonosetron is another exciting addition to our growing oncology product portfolio, representing another welt-advanced product that can be commercialized in the near term."

"Palonoseiron is our first product entry into the United States, and we are pleased to be working with MGI PHARMA for the North American distribution of this innovative product in the supportive cure segment of oncology." commented Riccardo Braglia, managing director of HEISINN We know that MGI PHARMA's proven commercial organization, its experienced oncology sales force and its present and future commitment to palonosetron's role within the 5-HT, antagonist marketplace will ensure the success of our new partnership."

About Palonosetron

When launched as a marketed product, palonosetron will be one of four products competing in the $1 billion North American market for 5-HT, antagonists. The extended half-life of palonosetron as compared to the other agents and the results of Phase 2 trials assessing efficacy beyond 24 hours differentiates palonesetron from the three currently marketed 5-HT, antagonists indicated for ClNV.

CINV is estimated to occur in 85 percent of cancer patients undergoing chemotherapy and can result in delay or even discontinuation of treatment, and the advent of 5-11 1 antagonists has revolutionized the management of nausea and vomiting experienced by cancer patients undergoing chemotherapy.

Palonosetron has been tested in a randomized, double-blind dose ranging Phase 2 trial at multiple sites throughout the U.S. that evaluated its efficacy and safety when administered in a single intravenous dose for the prevention of nausea and vomiting in patients receiving highly emetogenic chemotherapy.

Over 1,000 patients have participated in Phase 1 and Phase 2 trials of palonosetron. Based on these results, HELSINN Initiated a Phase 3 clinical trial program that is intended to enroll more than 1,900 patients in several well-controlled, double-blind trials comparing palonosetron to currently available 5-HT, antagonists – at approximately 80 centers in North America and Europe. Based on the extended half-life of palonosetron and the results of the Phase 2 trial, its efficacy wit be assessed over Day 2 through Day 5 following treatment, in addition to the primary efficacy measure of complete response during the 24-hour period after the start of chemotherapy. The most frequent adverse events associated with palonosetron are similar to those seen with other 5-HT, antagonists and include headache and constipation.

Under the terms of the exclusive license agreement. MGI PHARMA will make $11 million in upfront payments, already including the initial $5 million made upon signature of the letter of intent, and will make additional payments based on the achievement of certain milestones through the approval of palonosetron in the U.S. HELSINN will continue to fund and conduct all development of palonosetron MGI PHARMA will also pay royalties and product supply fees based upon net sales. HELSINN will supply finished product ready for distribution, the active ingredient of which is manufactured at HELSINN'S new state-of-the-art facility (HELSINN ADVANCED SYNTHESIS SA) dedicated to the production of high-potency active ingredients.

About MGI PHARMA

MGI PHARMA, INC. is an oncology-focused pharmaceutical company that acquires, develops and commercializes proprietary products that meet

patient needs and build shareholder value. MGI focuses its sales efforts solely in the United States and collaborates with other pharmaceutical or biotechnology companies for its products in international markets. For more information about MGI, please visit the Company's web site at www.mgipharma.com

BEGIN PRIVACY ENHANCED MESSAGE

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STREET 2: SUITE 110

CITY: BLOOMINGTON

STATE: MN

ZIP: 55438

BUSINESS PHONE: 6129357335

MAIL ADDRESS:

STREET 1: OPUS CENTER

STREET 2: 9900 BREN ROAD EAST SUITE 300E

CITY: MINNEAPOLIS

STATE: MN

ZIP: 55343

FORMER COMPANY:

FORMER CONFORMED NAME: MOLECULAR GENETICS INC

DATE OF NAME CHANGE: 19900812

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SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 8-K

Current Report Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): March 22, 2001

MGI PHARMA, INC.
(Exact name of registrant as specified in its charter)

Minnesota
(State or other jurisdiction of incorporation)

0-10736
(Comission File number)

41-1354647
(I.R.S. Employer identification No.)

6300 West old Shakopee Road, Suite 110,
Bloomington, MN 55438
(Address of principal executive offices)

Registrant's telephone number, including area code:
(957) 346-4200

Not Applicable
(Former name or former address, if changed since last report)

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ITEM 5. OTHER EVENTS

On April 6, 2001. MGI PHARMA, INC. (the "Company") announced that it had entered into definitive agreements with Helsinn Healthcare SA ("Helsinn"), pursuant to which Helsinn granted to the Company exclusive license and distribution rights to the product candidate palonosetron in the United States and its possessions and territories (Puerto Rico, United States Virgin Islands), and Canada and its provinces, possessions and territories. Under the terms of the license agreement. the company will make $11 million in initial payments, which amount includes an initial payment of $5 million made upon the execution of a letter of intent in October 2000, and will make additional payments to Helsinn based on the achievement of development milestones. The Company will also pay royalties to Helsinn based upon net sales. Under the terms of a related supply agreement, an affiliate of Helsinn will supply the company's requirements of finished product. The Company will pay the affiliate product supply fees based upon net sales. The term of each of the agreements is ten years from the launch of the commercialized product, unless earlier terminated by the parties.

The license agreement and the supply agreement are attached as Exhibits 99.1 and 99.2 to this report and are incorporated herein by reference. This

summary of the provisions of the agreements is not complete and is qualified in its entirety by reference to the agreements. The press release dated April 10, 2001 announcing the execution of definitive agreements is attached as Exhibit 99.5 to this report and is incorporated herein by reference.

On March 22, 2001, the Company announced in a press release that it had initiated a new Phase 2 clinical trial of the anti-cancer compound irofulven for patients with refractory or recurrent advanced epithelial ovarian cancer. The press release is Filed as Exhibit 99.3 to this report and is incorporated herein by reference.

On March 28, 2001, the Company announced in a press release that six presentations on irofulven's anti-tumor activity and mechanism of action were made at the American Association for Cancer Research meeting held on March 24-28, 2001. The press release is filed as exhibit 99.4 to this report and is incorporated herein by reference.

On April 12, 2001, the Company announced in a press release that it had initiated an additional Phase 2 clinical trial of irofulven using an intermittent dosing schedule to treat hormone-refractory prostate cancer patients. The press release is filed as Exhibit 99.6 to this report and is incorporated herein by reference.

On April 18, 2001, the Company reported its earnings for the first quarter of 2001 in a press release, which is filed as exhibit 99.7 to this report and is incorporated herein by reference.

On April 25, 2001, the Company announced in a press release that a parent for the "Inhibition of DNA Methyltransferase" was recently granted to

MethylGene Inc., the partner with whom the Company has an exclusive North American license, research and development agreement for inhibitors of DNA methyltransferase. The press release is filed as Exhibit 99.6 to this report and is incorporated herein by reference.

ITEM 7. FINANCIAL STATEMENTS AND EXHIBITS

(c) EXHIBITS.

*99.1 License Agreement, dated as of April 6, 2001, between Helsinn Healthcare SA and MGI PHARMA, INC.

*99.2 Supply and Purchase Agreement, dated as of April 6, 2001, between Helsinn Birex Pharmaceuticals Ltd. and MGI PHARMA, INC.

99.3 Press Release, dated March 22, 2001.

99.4 Press Release, dated March 28. 2001.

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99.5 Press Release. dated April 10, 2001.

99.6 Press Release, dated April 12, 2001.

99.7 press Release, dated April 18, 2001.

99.8 Press Release, dated April 25, 2001.

* Pursuant to Rule 24-b of the Securities Exchange Act of 1934, as amended, confidential portions of Exhibits 99.1 and 99.2 have been deleted and filed separately with the Securities and Exchange Commission pursuant to a request for confidential treatment.

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SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, hereunto duly authorized,

April 25, 2001

MGI PHARMA INC.

By: /s/ William C. Brown
William C. Brown
Chief Financial officer

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Exhibit 99.1

License Agreement between HELSINN HEALTH CARE SA and MGI Pharma, INC. for PALNOSETRON

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THIS AGREEMENT (hereinafter called "Agreement") is effective as of this 6th day of April 2001 (hereinafter called "Effective Date") between HELSINN HEALTHCARE SA, a corporation organized and existing under the law of Switzerland and having its registered office at Via Pian Scairolo, 6912 Pazzallo, Switzerland (hereinafter called "HHC") of the one part, and MGI PHARMA, INC., a corporation organized and existing under the law of the state of Minnesota, United States of America and having its registered office at 6300 West Old Shakopee Road, Suite 110, Bloomington, MN 50418-2318, USA (hereinafter called "MGI"), of the other part.

RECITALS

a. HHC carries on business as a licensing company, product developer and pharmaceutical trader and. in particular for the purpose of this Agreement, has in-licensed from the companies Syntex (U.S.A.) Inc. and F. Hoffman-La Roche AG by means of a License Agreement dated June 23, 1996 (hereinafter, the "Syntex Agreement") world-wide exclusive rights to certain patents and know-how to make, have made, develop, register, market, distribute and sell, directly

or indirectly, the Compound (as hereinafter defined) and pharmaceutical preparations containing said compound as active pharmaceutical ingredient.

b. MGI carries on business as a pharmaceutical company and, in particular for the purpose of this Agreement, represents that it is a reputable pharmaceutical company, having a size and a position on the market adequate to effectively market, distribute and sell the Products (as hereinafter defined) and that it has the necessary sales force to successfully sell the Products in the Field throughout the Territory (as hereinafter defined).

c. Prior to entering into discussions with HHC, MGI possessed no technology and limited information of its one (including publicly available information) relating to the Compound and/or the Products. The Parties entered on 25th May 2000 into a Secrecy Agreement by means of which HHC disclosed to MGI confidential information and data relating to the Compound and Products.

d. The Parties entered on October 5th, 2000 into a Letter of Intent on which basis they have performed respective appropriate due diligence for the purpose of establishing their interest

and willingness to enter into this Agreement, and hereby confirm that (i) each has been provided with full and complete access to such information as they deemed necessary or appropriate to conduct the diligence, and (ii) such due diligence has been completed to their full satisfaction.

e. MGI now wishes to acquire the right to act as HHC's licensee and distributor for the products in the Territory and HHC is willing to so appoint MGI under the terms and conditions hereinafter set forth.

f. The Parties agree that this preamble constitutes an integral part of this Agreement and all capitalized terms used in this preamble shall have the meaning as defined in Article 1 hereafter.

NOW, THEREFORE, in Consideration of the foregoing and of the mutual covenants and conditions herein contained, the Parties hereby agree as follows:

ARTICLE 1 - DEFINITIONS

The following terms as used in this Agreement have, unless the content clearly indicates otherwise, the following meanings:

1.1 "Accounting Period" means the quarters ending 31st March, 30th June, 30th September and 31st December in each year throughout the term of this Agreement.

1.2 "Affiliate" means an organization that, whether now or in the future, controls, is controlled by or is under common control with a Party. For the purposes of this definition, the terms "controls," "controlled by," and "under common control with" as used with respect to any Party, means the possession (directly or indirectly) of fifty percent or more of the voting stock or other equity interest of a subject entity with the power to vote, or the power in fact to control the management decisions at such entity through the ownership of securities or by contract or otherwise.

1.3 "Compound" means the active pharmaceutical ingredient (3as-2-[(S)-1-Azabicyclo[2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1H-benz[de]isoquinoline

hydrochloride, having the generic name palonosetron hydrochloride (INN) for use in human medicine.

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1.4 "FDA" means the U.S. Food and Drug Administration or any successor agency.

1.5 "Field" means the prevention of chemotherapy induced nausea and vomiting (CINV) in terms of the Regulatory Authorities approved indication.

1.6 "HHC's Other Distributors" means any distributor and/or licensee appointed by HHC to promote and sell pharmaceutical preparations containing the compound in any country of the world outside the Territory and outside the Field in the Territory.

1.7 "Improvements" means all improvements, modifications or developments relating to the Field and/or to the Product forms subject of this Agreement, which might improve the quality or improve consumer acceptance and/or patient compliance of the products. For clarity, except to the extent MGI has exercised its right of first refusal under Article 2.6, "Improvements" shall not include dosage forms other than the intravenous ("I.V.") formulation as shall be described in the Registration and/or indications other than within the Field.

1.8 "Know-how" means valuable, secret and substantial information regarding the Products in the Field, including but not limited to documentation and information on file with the FDA or other Regulatory Authority in support of the Registration, which may be necessary, useful or advisable to enable MGI to promote, market and sell the Products in the field in the Territory, as far as controlled by or available to,

and not prohibited to be disclosed or licensed by, HHC, all as listed in the First Appendix hereto and as is or will be specified in the documentation which HHC has delivered or will deliver to MGI after execution of this Agreement.

1.9 "Net sales" means the gross sales in local currencies of all Products sold in the territory by MGI and/or its Affiliates, including any local Affiliate in Canada, for arm's lenghth sales to any non-Affiliated third party less those normal and customary deductions made under Generally Accepted Accounting Principles to arrive at Product sales.***

*** Denotes confidential information that has been omitted from the exhibit and filed separately, accompanied by a confidential treatment request, with the Securities and Exchange Commission pursuant to Rule 24b-2 of the Securities Exchange Act of 1934.

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1.10 "Parties" means HHC and MGI and "Party" means either of them as the content indicates.

1.11 "Patent" means (a) the patents and the parent applications licensed or assigned to HHC pursuant to the Syntex Agreement, as listed in the Second Appendix hereto; (b) all patents in the Territory issuing from said applications; (c) any additions, divisions, continuations, continuations-in-part, amendments, amalgamations, reissues and re-examinations of such applications or patents in the Territory; (d) any confirmation, importation and registration patents thereof in the Territory, and (e) any extensions and renewals of all such patents and patent applications in

the Territory in whatever legal form and by whatever legal title they are granted.

1.12 "Products" means the pharmaceutical preparations for human use in I.V. dosage form, containing the compound as an active ingredient in the formulation that will be described in the Registration and such other formulations for which MGI exercises its right of first refusal pursuant to Article 2.6. The Current formulation as submitted to the Food and Drug Administration of the United States of America in the IND 39,797 Amendment # 64 and to the Therapeutic Products Programme of Canada in the IND 9427-H0836-21C is described in the Third Appendix hereto.

1.13 "Registration" means any official approval, or authorization by the Competent Regulatory Authority of each country in the Territory, which is legally required to lawfully market the Products in the Territory, including, without limitation, any governmental price approval or reimbursement approved under a national health insurance system.

1.14 "Regulatory Authority" means, with regard to the United States of America the United States Food and Drug Administration (FDA) and, with regard to Canada the Therapeutic Products Programme, or any other agency which shall be responsible for the issuance of the Registration throughout the term of this Agreement.

1.15 "Territory" means the United States of America and its possessions and territories (Puerto Rico, United States Virgin Islands), and Canada and its provinces, possessions and territories.

1.16 "Trademark" means the trademark DEDYS(R) or ONICIT(R), which are and shall be HHC's property, or under another trademark to be selected by the Parties, it being understood that HHC shall bear reasonable documented expenses in connection with such selection, and which shall be HHC's property.

ARTICLE 2 - GRANT OF RIGHTS AND COMPETITION

2.1 Subject to all terms and conditions of this Agreement, HHC hereby grants MGI, and MGI hereby accepts, an exclusive non-transferable and non-assignable (except as provided at Article 2.8 here below with regard to distribution, promotion and sale of the Products in the Field by a local Affiliate of MGI in Canada), royalty-bearing license under the Patents and to use the Know-how, to distribute, promote, market and sell the Products in the Territory for the Field.

Moreover, subject to all terms and conditions of this Agreement, HHC hereby grants MGI, which hereby accepts, an exclusive, non-transferable and non-assignable (except as provided at Article 2.8 here below with regard to distribution, promotion and sale of the Products in the Field by a local Affiliate of MGI in Canada). royalty-bearing license to affix the Trademark to the Products and to use it in connection with the distribution. promotion, marketing and sale of the products in the territory for the Field.

2.2 The exclusivity granted pursuant to this Article 2 means that only MGI may be licensed by HHC to distribute, promote, market and sell the Products in the Territory for the Field.

***

2.3 MGI agrees not to knowingly market, ship, distribute, promote, sell or otherwise put into circulation the Products outside the Territory and/or outside the Field and to expressly and consistently inform distributors and/or wholesalers for the products, by warning letters or

***Denotes confidential information that has been omitted from the exhibit and filed separately, accompanied by a confidential treatment request, with the Securities and Exchange Commission pursuant to Rule 24b-2 of the Securities Exchange Act of 1934.

other appropriate and effective means, that the distribution and sale of the Products outside the Territory and/or outside the Field is prohibited and to enforce such prohibition as and when necessary. In the event that MGI enters into any agreements with its distributors and/or wholesalers for the Products, it shall use commercially reasonable efforts to include in any and all said agreements appropriate provisions prohibiting, to the maximum extent permissible under applicable laws and regulations, that the Products are distributed outside the Territory and/or outside the Field, and to enforce such provisions as and when necessary. Moreover, MGI undertakes to pass on to HHC any request for the Products coming to MGI from any party or for sale outside the Territory.

2.4 ***

2.5 MGI acknowledges and agrees that it shall not have the right to manufacture directly or indirectly, the compound and/or the Products. In order to maintain at all times the highest quality for the

Products and to ensure a scientifically proper and safe exploitation of the licensed Know-how and Patents and in order to maintain and to protect the goodwill of the Trademark MGI undertakes to purchase all of its Products' requirements exclusively from a source indicated or approved by HHC; provided that such source meets all requirements of applicable Regulatory Authorities and specifications for the Products applicable in the Territory.

2.6 The Parties hereby acknowledge and agree that the development and marketing of an oral formulation or the Compound will be useful for enlarging The market f pharmaceutical preparations containing the compound in the Field and undertake to discuss in good faith on the timing, costs and any other conditions relevant to the development, registration and marketing of such oral formulation. In addition. HHC shall offer to MGI a first negotiation right for the Territory (or some portion thereof) to distribute, promote, market and sell any new dosage form(s) and/or formulation(s) (other than the I.V. formulation as shall be described in the Registration) of the Products in the field (i) becoming available to HHC throughout the term of this Agreement and which HHC is free to offer in the Territory (or a portion thereof) or (ii) which development nod marketing pay be deemed of interest for the Parties or any of them.***

*** Denotes confidential information that has been omitted from the exhibit and filed separately, accompanied by a confidential treatment request, with the Securities and Exchange commission pursuant to rule 24b-2 of the Securities Exchange Act of 1934.

2.7 MGI acknowledges that there are or there may be different uses or indications of the Products and that the rights and licenses hereby granted by HHC are limited to the Field. HHC retains the right to, and shall be free to exploit at its own discretion into and outside the Territory, any and all uses or indications of the Products outside the Field, in whichever dosage form and/or formulation HHC may deem fit, including but not limited to I.V., and MGI shall have no rights in any respect whatsoever to such uses and/or indications outside the Field, provided that HHC shall not be entitled to use the Trademark or trademarks which are confusingly similar to the Trademark in respect of marketing and sale in the Territory of said uses and/or indications of the Products outside the Field; provided that such exploitation does not conflict with, or otherwise violate the terms and conditions of this Agreement.

2.8 MGI shall not have the right to sublicense or otherwise transfer any of its rights and/or obligations hereunder; provided that MGI shall be entitled to engage co-promotion partners in the United States, subject to HHC's prior approval, not to be unreasonably withheld. Moreover, MGI shall not have the right to sub-contract any of its rights and/or obligations hereunder, provided however that MGI shall be entitled to have the logistics and warehousing activities (excluding however invoicing and billing to customers) relevant to the Products carried out by its Affiliates or by third parties in the Territory. It is understood

that MGI shall have the right to have the Products distributed, promoted and sold in Canada by its local Affiliate whose name and address, and any change thereof, shall be timely notified to HHC.

MGI undertakes and warrants that its Affiliate in Canada shall strictly comply with MGI's applicable obligations and warranties stated in this Agreement and any breach of such obligations and/or warranties by such Affiliate shall be regarded in all respects and in particular for the purposes of Articles 11 and 17 hereunder, as a breach by MGI. Correspondingly, MGI shall be fully responsible towards HHC for any action and/or omission of its said Affiliate, and shall defend, indemnify and keep HHC wholly free and harmless from any connected claims, damages, liabilities, losses, costs and/or expenses. Moreover, MGI expressly undertakes and warrants that any agreement with respect to the Products between itself and its Affiliate in Canada shall be fully consistent with this Agreement and undertakes to send to HHC, upon HHC'S written request, a copy of any said executed agreement (with economic terms redacted) for the purpose of enabling HHC to verify compliance with terms and conditions hereof.

MGI shall be permitted to disclose to its Affiliate in Canada such Know-how and other relevant information to the extent strictly necessary and appropriate to correctly carry out its obligations hereunder, provided however than any such disclosure shall be made only under a confidentiality agreement, for the benefit of and approved in writing by HHC, having terms at least as restrictive as those provided herein.

2.9 MGI shall not enter into any agreement with third parties with respect to the Compound and/or the

Products, except as may be necessary for the purpose of a full and correct exploitation of the Products in accordance with all terms and conditions of this Agreement. upon HHC's written request, MGI shall send to HHC a copy of any said executed agreement (with economic terms redacted) for the purpose of enabling HHC to verify compliance with terms and conditions hereof. Nothing in this Agreement shall be construed as giving MGI any right to use or otherwise deal with the Know-how, the Patents and/or any other information received hereunder for purposes other than those of distributing, promoting, marketing and selling the Products in the Territory for the Field in accordance with the terms and conditions of this Agreement. In particular, and without limiting the generality of the foregoing, MGI hereby undertakes not to file any application for the Registration of generics of the Products in the territory or outside the Territory throughout the term of this Agreement.

2.10 MGI shall promptly inform HHC of any misappropriation, or threatened or presumed misappropriation of the Know-how which comes to its attention. HHC will decide on the steps to be taken after having discussed the case with MGI and MGI shall assist, bearing

exclusively its own internal costs and HHC bearing MGI's reasonable out-of-pocket costs, HHC in taking legal action, if deemed necessary by HHC, against such misappropriation.

2.11 Each Party shall promptly and fully inform the other if it has a reasonable basis to believe that there have been unauthorized sales of the Products into or

outside the Territory, and shall use practical efforts with all such persons to act consistently with the terms and conditions of this Agreement.

2.12 In the event that MGI fails to respect the limitations of the licenses granted under this Article 2 and MGI or its Canadian Affiliate knowingly distributes Products outside the Territory and/or outside the Field. or fails to enforce appropriate prohibitions on such distribution of Products outside the Territory and/or outside the Field by its distributers and/or wholesalers in accordance with Article 2.3 here above, MGI shall be deemed to be in material default, and HHC shall have the right, in its sole discretion, to terminate this Agreement by written notice to MGI, which breach is not cured within a sixty (60) days notice period.

ARTICLE 3 - EXCHANGE OF INFORMATION AND IMPROVEMENTS

3.1 Throughout the term of this Agreement, HHC shall supply MGI in writing and free of charge with any relevant Know-how, in addition to that already supplied at the Effective Date hereof, which may be or become available to HHC and which HHC is free to disclose. Notwithstanding the foregoing, nothing in this Agreement shall require HHC to obtain additional Know-how from third parties.

In the event that MGI should require technical assistance in connection with its initial sale of the Products in the Territory, HHC will use its commercially reasonable efforts to assist MGI for reasonable periods of time and at times convenient to HHC.

3.2 MGI shall supply HHC in writing or by any other appropriate support, free of charge, with any and

all technical and/or scientific information and data relating to the Products and/or the Compound, as soon as they are or become available to MGI throughout the term of this Agreement. MGI shall communicate any such information and data to HHC and MGI shall use such information and data for the purpose of the distribution, promotion and sale of the Products in the Territory for the Field in accordance with the terms and conditions of this Agreement. HHC shall have the right to use such information and data for the purpose of its business and to disclose the same to HHC's Affiliates and to HHC's other Distributors, which in turn shall have the right to use them for the purpose of the distribution, promotion

and sale or pharmaceutical preparations containing the compound outside the Territory and outside the Field in the Territory.

3.3 MGI's rights hereunder shall include any Improvement carried out by or which may be discovered, developed, invented or acquired by HHC, for use in accordance with the terms and conditions of this Agreement. Any Improvement which may be carried out by or which may be discovered, developed, invented or acquired by MGI, its officers, agents or employees, may be used by MGI for the purpose of the distribution, promotion and sale of the Products in the territory for the Field in accordance with the terms and conditions of this Agreement and will be promptly disclosed and is hereby automatically licensed free of charge to HHC on an exclusive basis even as to MGI (except for those MGI'S activities described here above) and HHC shall have the right to sublicense the

above Improvements to HHC's Affiliates and to HHC's Other Distributors for use outside the Territory and outside the Field in the Territory MGI shall not incur any obligation to any third party which may prohibit or impair its ability to disclose and license Improvements to HHC.

3.4 All Know-how, Improvements and/or other information and data disclosed to MGI hereunder are at all times and shall after expiration or termination of this Agreement for any reason remain HHC'S sole and exclusive property.

ARTICLE 4 - DEVELOPMEHT AND REGISTRATION OF PRODUCTS

4.1 MGI hereby acknowledges and agrees that

4.1.1 at the Effective Date of this Agreement the Products are under development by HHC for the purpose of submitting the relevant Registration application to the Regulatory Authorities of the Territory,

4.1.2 the development of the Products by HHC may be interrupted or discontinued by HHC as set forth in Article 4.2, if said development becomes commercially unreasonable, or the relevant results may be negative or unfavorable,

4.1.3 the development mark presently carried out will not necessarily result in the grant of the Registration of the Products and

4.1.4 HHC makes no warranty and nothing in this Agreement may Or shall be construed as a warranty by HHC that the Products obtain the Registration or that a

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Product can be developed and registered from the know-how and MGI shall have no claim against HHC arising out of any delay or refusal by the Regulatory Authorities to issue the Registration in any way whatsoever.

4.2 HHC will use commercially reasonable efforts to complete the development of the Products in accordance with the Development Chart attached as Fourth Appendix hereto and, subject to satisfactory development of the Products and provided that no unforeseeable events occur or additional requests are made by the Regulatory Authorities with respect to the development of the Products described in the Development Chart hereto attached, to file the NDA for the Products in the United States of America not later than ***. ***

*** Denotes confidential information that has been omitted from the exhibit and filed separately, accompanied by a confidential treatment request, with the Securities and Exchange Commission pursuant to Rule 24b-2 of the securities Exchange Act of 1934.

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4.3 Applications for the Registration in the Territory shall be filed by HHC in its own name and at its own expenses, HHC shall also pay all administrative fees for the maintenance in force of the Registration throughout the term of this Agreement.

4.4 MGI expressly acknowledges and agrees that HHC is and shall at all times remain the sole and exclusive owner of the Registrations and that ownership of said Registrations and any and all rights,

title and interest (including any accompanying goodwill) are, and shall at all times remain, vested in HHC.

4.5 After approval of the NDA for the Products in the United States and compliance by MGI with the provision of Article 7.1.5 hereunder, MGI shall be appointed by HHC as HHC's agent with respect to the NDA for the Products in the Field ("FDA Agent") and shall manage and carry out on behalf of the HHC all relevant communications and relations with the FDA. In addition, MGI shall be entitled to participate in all negotiations and discussions between HHC and the FDA regarding any labeling for the Products in the Field with the exception of those activities specifically listed in the Fifth Appendix hereto, which shall be performed and carried out by HHC. Nothing in this Agreement precludes HHC from appointing an FDA Agent on different NDAs for products other than the Products (including, without limitation, any new dosage form(s) and/or formulation(s) of the Products in the Field under the terms provided at Article 2.6 hereabove) or for the Products outside the Field or from changing HHC's corporate agent in the United States ("U.S. Agent") at any time.

All said activities, communications and relations as well as MGI's role of HHC's FDA Agent as described above shall be performed by MGI in close coordination with HHC, directly or through third parties, as the holder of the Registrations. In particular, MGI shall copy within 48 hours and keep HHC fully and promptly informed, throughout the term of this Agreement, of all communications received from the Regulatory Authorities of the Territory concerning the Products and/or the Compound. Without prejudice to full compliance by both Parties with any obligations

established by applicable laws and regulations of the Territory with regard to adverse events reporting and any other deadlines set by Regulatory Authorities, any and all communications to Regulatory Authorities relevant to the Compound and/or the Products and connected with the activities described above, shall be sent by MGI only after the relevant contents have been described above, shall be sent by MGI only after the relevant contents have been discussed with and approved in writing by HHC, which approval shall be deemed to have been given if HHC does not otherwise respond within ten working days in Switzerland of receipt of such proposed communication; provided however, that MGI shall not be required to obtain such prior approval with respect to those mutually agreed routine administrative communications

with the FDA. MGI further undertakes and warrants that it shall at all times strictly comply with any and all laws, rules and regulatory requirements in force in the Territory in connection with the activities, communications and relations contemplated herein.

4.6 MGI shall store and distribute, and shall cause the Products to be stored and distributed according to applicable current Good Manufacturing Practice or any other applicable laws and regulations. MGI shall permit HHC's representatives, during normal business hours and upon three business days advance notice in writing, to inspect those areas of the warehouses of MGI, its Affiliates and distributors where the Products are stored, for the purpose of verifying compliance with applicable laws and regulations as well as with this Agreement.

4.7 If material alterations, modifications or amendments of this Agreement or of the Products are imposed by any Regulatory Authority as prerequisites for the grant or the continuation of the Registration of any of the Products, or if Registration of any of the Products is suspended or withdrawn by any said Regulatory Authority, each Party shall notify the other promptly after receipt of notification from such Regulatory Authority and the Parties shall endeavor to agree upon a reasonable and mutually acceptable resolution thereof. In the event that the Parties are unable to agree upon such a resolution. HHC shall have the right at its sole discretion, upon written notice to MGI, to delete the Product or products in question from this Agreement or to take any other measure which it reasonably deems necessary or advisable and, if necessary, to terminate this Agreement, in which case the consequences provided for at Article 17.6, 17.7 and 17.8 hereunder shall apply, it being understood that in any case, except as expressly provided in Article 11 of, this Agreement, HHC shall have no obligation, liability or responsibility whatsoever to compensate, indemnify or reimburse MGI for any payments, damages, losses, costs or expenses incurred by MGI in connection with this Agreement or termination hereof and that the payments already effected by MGI at the effective date of termination pursuant to Article 7 hereunder shall be retained by HHC.

4.8 MGI shall collaborate with and assist HHC and/or any of HHC's Other Distributors for the purpose of obtaining Registrations outside the Territory and/or, outside the Field in the Territory. Such collaboration and assistance shall include, but not be limited to, doing all such acts as may be required by HHC for the purpose of permitting access

and maximum use by HHC and/or HHC's Other Distributors of the documentation and results of the activities described at Article 4.5 hereabove and of development work on the Products carried out by MGI pursuant to Article 5.3 here below. HHC shall reimburse MGI for reasonable out-of-pocket expenses incurred in providing such collaboration and access.

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4.9 Each Party undertakes to give the other Party full, accurate and prompt information in writing with regard to adverse events associated with the use of the Products, whether or not ascertained to be definitely attributable to the Products or the Compound, in strict accordance with the procedures and rules established in the Sixth Appendix attached to this Agreement.

4.10 In the event of a recall, complaint, field alert, product withdrawal relevant to the Products marketed by MGI in the Territory, the Parties shall strictly follow the procedures and rules established in the Seventh Appendix to VHS Agreement.

4.11 MGI shall permit HHC and/or any authorized representative or consultant of HHC to enter MGI's premises, as well as the premises of MGI's Affiliates and/or distributors in the Territory, during normal business hours and upon at least three (3) business days advance notice, to audit and verify compliance by MGI its Affiliates and distributors with regulatory and other requirements in force in the territory, as well as with this Agreement, with respect to all aspects related to Registration and to correct and safe distribution, promotion, marketing and sale of the Products in the Territory or in connection with any recall contemplated by Article 4.10 hereabove.

Such audit shall include, without limitation, the right to examine any interval procedures or records of MGI, its Affiliates and distributors relating to the Products. MGI shall give and shall cause its Affiliates and distributors to give, all necessary assistance for a full and correct carrying out of the audit by HHC. No such monitor and/or audit by HHC shall relieve MGI, its Affiliates and distributors of any of their obligations under this Agreement in any way whatsoever.

In the event that any Regulatory Authority or any other competent authority of the territory carries out or gives notice of its intention to carry out any inspection or audit of MGI, its Affiliates or distributors or otherwise takes any action in relation to the Products, MGI shall immediately notify HHC in full details and shall use commercially reasonable efforts to insure that HHC shall have the right to be present at and to participate in any such inspection or audit.

ARTICLE 5 - POST-REGISTRATION DEVELOPMENT

5.1 HHC shall use commercially reasonable efforts to provide any further clinical and product development that may be requested by any Regulatory Authority in the Territory for the maintenance of the Registration.

5.2 MGI acknowledges that the performance of additional post-approval trials may be needed to market Products more effectively in the Territory.

5.3 MGI shall not undertake nor carry out any trial relevant to the Products without the prior written

approval of HHC. MGI shall perform and fund any trials mentioned at article 5.2 hereabove in accordance with a development plan to be agreed upon in advance with HHC. All relevant protocols shall have to be discussed and approved in writing by HHC. Any and all data, information and know-how whether patentable or not, arising from said trial will be promptly disclosed and is hereby automatically licensed free of charge to HHC on an exclusive basis even as to MGI (provided that MGI shall have the right to use such data, information and know-how solely for the purpose of the distribution, promotion and sale of the Products in the Territory for the Field in accordance with the terms and conditions of This Agreement) and HHC shall have the right to sublicense said data, information and know-how to HHC's affiliates and to HHC's Other Distributors for use outside the Territory and outside the Field in the Territory. MGI shall not incur any obligation to any third party which may prohibit or impair its ability to disclose and license said data, information and know-how to HHC. In addition, HHC shalt use commercially reasonable efforts to put at MGI's disposal for use in the distribution, promotion, marketing and sale of the Products in the Territory for the Field in accordance with the terms and conditions of this Agreement, any post-registration trial carried out by HHC's Other Distributors with regard to the Products.

ARTICLE 6 - TRADEMARK OF PRODUCTS

6.1 The Products shall be distributed, promoted, marketed and sold by MGI in the Territory exclusively under the Trademark.

6.2 MGI shall use the Trademark exclusively in connection with and for the purpose of the distribution promotion, marketing and sale of the Products for the

Field in the Territory. MGI acknowledges that it shall be entitled to no rights whatsoever in the Trademark except as is specifically granted pursuant to this agreement and then only to the extent of the express grant.

6.3 HHC shall register MGI, and MGI shall assist HHC in having MGI registered, as a licensee in the Trademark Register or the Territory as necessary and useful, in particular regarding the recordation as "Registered User" where corresponding legal provisions exist. Such registration shall be cancelled after expiration or termination of this Agreement for any reason upon the request of HHC.

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6.4 HHC's trade name and logo shall appear on all Products packaging, labels and inserts and other materials which MGI uses for the distribution, promotion, marketing and sale of the Products in such form and manner as shall be approved by HHC in writing in compliance with all requirements of applicable Regulatory Authorities.

6.5 MGI shall make no use of the Trademark except in the form and with the graphics authorized in advance by HHC. MGI shall for each use feature a prominent notice and acknowledgment of the registered Trademark ownership and license by HHC in conjunction with all usage of the Trademark. HHC shall have the right to review and approve all intended uses of the Trademark in any packaging, inserts, labels, promotional or other materials relating to the Products prior to actual use thereof.

6.6 MGI will not alter, obscure, remove, conceal or otherwise interfere with any markings, names, labels or other indications of the source of origin of the Products which may be placed by HHC on the Products.

6.7 MGI will not use nor apply for registration of any trademark, trade-name or logo in connection with the Products, nor shall it use or apply for registration of any trademark, logo or design which includes the Trademark, alone or in combination, in or outside the Territory, without the prior written authorization of HHC, which authorization HHC may withhold in its sole and absolute discretion.

6.8 Nothing contained in this Agreement shall be construed as giving MGI a right to use the Trademark or Portions thereof or any word confusingly similar to the Trademark or the name "Helsinn" as MGI'S corporate name or any part thereof. Throughout the term of this Agreement and thereafter, MGI shall not use nor apply for registration of, any mark, logo or design, in or outside the Territory, which is, or is likely to be, confusingly similar to, or could cause deception or mistake with respect to, the Trademark or to the name "Helsinn" on any pharmaceutical or chemical or healthcare product or service.

6.9 Nothing contained in this agreement shall be construed as giving MGI the right to use the Trademark outside the Territory or for any other product than the Products and HHC may use, or license others to use the Trademark in all jurisdictions outside the Territory.

6.10 The Trademark shall always be used together with the sign "R" or the sign "TM" or such other

customary symbol or legend which identifies correctly the status of the Trademark.

6.11 MGI recognizes the exclusive rights of HHC regarding the Trademark and acknowledges that it shall not acquire any rights in respect of the Trademark of HHC in relation to the

Products or of the goodwill associated therewith and that all such rights and goodwill are, and shall at all times remain, vested in HHC.

6.12 HHC shall keep in force the Trademark by paying the necessary fees throughout the term of this Agreement and by using all reasonable efforts to defend any action or proceeding for cancellation of the Trademark, bearing the whole cost thereof and MGI shall render any reasonable assistance in this respect.

6.13 MGI shall promptly notify HHC of any threatened or presumed significant counterfeits, copies, imitations, simulations of, or infringement upon, the Trademark or the name "Helsinn" or of any other act or unfair competition which comes to its attention. HHC will decide on the steps to be taken after having discussed the case with MGI and MGI shall glee its full co-operation therefor at HHC's expense, should it occur that HHC for any reason decides not to defend the Trademark, then MGI shall have the right to take appropriate action for defending the Trademark in its own name with the consent of HHC. In such case, MGI shall bear all the costs and shall be entitled to retain any compensation paid by third persons in this respect.

6.14 MGI acknowledges that HHC has no adequate remedy under this Agreement or at law in the event that MGI were to use the Trademark in a manner not authorized by this Agreement and that HHC would, in such circumstances, be entitled to specific performance, injunctive or other equitable relief, including interlocutory and preliminary injunctive relief.

6.15 MGI shall be entitled to mark the Products packaging, labels and inserts with the MGI name and logo, in a manner reasonably acceptable to HHC.

ARTICLE 7 - COMPENSATIONS BY MGI

7.1 As consideration for the right granted and information disclosed under this Agreement, in addition to the amount of USD5,000,000 (United States Dollars five million) which has been paid by MGI to HHC in accordance with the Letter of Intent mentioned at recital (d) here above. MGI shall pay to HHC, upon occurrence of the following events, the following milestone payments, which shall not be refundable nor creditable towards future royalties:

7.1.1 At signature of this Agreement, MGI shall pay to HHC USD6,000,000 (United States Dollars six million), of which up to 50% may, at MGI's option, be paid in freely tradable shares of MGI common stock as better specified at Article 7.7 hereunder;

7.1.2 Six months after execution of this Agreement, MGI shall pay to HHC USD ***;

7.1.3 At Type B pre-NDA meeting with the FDA, MGI shall pay to HHC USD ***;

7.1.4 At NDA filing in the United States of America, MGI shall pay to HHC USD *** of which up to 50% may at MGI's option, be paid in freely tradable shares of MGI common stock as better specified at Article 7.2 hereunder;

7.1.5 At NDA approval in the United States of America, MGI shall pay to HHC USD ***.

The above milestone payments shall be paid by MGI to HHC by wire transfer of immediately available funds to an account designated in writing by HHC; provided that the payments described at Articles 7.1.2 and 7.2.3 shall be paid pursuant to the terms of an Escrow Agreement among the Parties and U.S. Bank Trust Association in the Form attached as Appendix 8 hereto, dated as of the effective Date hereof. The milestone payments described at Articles 7.1.1, 7.1.2, 7.1.3, 7.1.4 and 7.1.5 shall be paid within 15 (fifteen) days of occurrence of the relevant event. Failure to pay any of the milestones on a timely basis shall entitle HHC to terminate this Agreement if MGI fails to cure such breach within a 15 (fifteen) days notice period.

7.2 MGI agrees to promptly inform HHC in writing as soon as it elects to effect part of the milestone payments under Articles 7.1.1 and 7.1.4 hereabove in freely tradable shares of MGI common stock. In this case, MGI shall issue to HHC such number of freely tradable shares of MGI common stock calculated by dividing the amount to be paid in MGI common stock by the average of the closing prices for such MGI common stock (as reported in The Wall Street Journal or, if not reported therein, in another mutually agreed upon authoritative source for the *** trading days before the date of payment of the related milestone payment (the "original Price"). MGI shall deliver the certificate representing such shares to HHC by

overnight courier within five (5) business days after such date of payment. Such shares shall be duly authorized, validly issued, fully paid and non-assessable and shall be free and clear of any and all liens, claims or other encumbrances. Notwithstanding anything contained herein to the contrary. MGI shall not be entitled to elect to satisfy its payment obligation under Articles 7.1.1 or 7.1.4, as the case may be, in freely tradable shares of MGI common stock, if, at the time that the payment becomes due pursuant to Article 7.1.1 or Article 7.1.4 above, as the case may be, the ***

*** Denotes confidential information that has been omitted from the exhibit and filed separately, accompanied by a confidential treatment request, with the Securities and Exchange Commission pursuant to Rule 246-2 f the Securities Exchange Act of 1934.

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common stock of MGI is not listed on The NASDAQ national market System ("NASDAG/NMS") in accordance with the NASDAQ/NMS requirements set for continued Listing - Standard 2. HHC acknowledges that any shares received from MGI in payment of its milestone payment obligations under Articles 7.1.1 or 7.1.4 of this Agreement will be "restricted securities" within the meaning of Rule 144 under the U.S. Securities Act of 1933, and that such shares will not be transferable in the U.S. markets unless and until such shares are either registered under the U.S. Securities Act of 1933 on an exemption from such registration requirement is available. MGI agrees that, unless a registration statement enabling such shares to be freely tradable by HHC upon receipt has

been filed by MGI and declared effective by the U.S. Securities and Exchange Commission and HHC has received reasonable assurances that MGI will maintain the effectiveness of such registration statement until HHC fully liquidates such shares in accordance with the restrictions contained in the last sentence of this Article 7.2, in each case prior to the date of delivery of such shares, then MGI shall not be entitled to elect to make part of the milestone payment under Articles 7.1.1 or 7.1.4 in shares of MGI common stock. MGI and HHC hereby acknowledge that, in connection with any such registration of shares of MGI common stock, MGI and HHC will use their reasonable best efforts to negotiate in good faith a registration rights agreement for such registration on terms reasonable and customary for such agreements. ***. Notwithstanding the filing and effectiveness of such registration statement, HHC agrees that, in connection with any sale of such MGI shares on the NASDAQ/NMS (or on any securities exchange or other public trading market on which MGI common stock is than traded), the number of shares of MGI common stock sold by HHC on any day will not exceed 10% (ten percent) of the average daily trading volume of MGI common stock in that market for the five trading day period ending two trading days prior to the date of such sale; provided, however, that (i) any shares sold by HHC in one or more block sales of at least 20,000 shares each which are effected through a market maker for MGI common stock shall not be counted for purposes of the foregoing volume

*** Denotes confidential information that has been omitted from the exhibit and filed separately, accompanied by a confidential treatment request, with the Securities and Exchange Commission pursuant to Rule 246-2 of the Securities Exchange Act of 1934.

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limitations, and (ii) such volume limitations shall however not apply to the extent that they require HHC a period longer than 90 (ninety) days from the first sale of MGI's shares by HHC to sell MGI's shares.

7.3 In addition to the above milestone payments, MGI shall pay running royalties as follows:

7.3.1 in consideration of the license granted hereunder on the Know-how, MGI shall pay to HHC or HHC's nominee a royalty of *** on all Net Sales throughout the term of this Agreement. It is expressly agreed that in case the Know-how becomes publicly known other than by action of HHC, the above royalty shall continue to be payable throughout the term of this Agreement, without prejudice to the payment to HHC of additional damages in case the Know-how becomes publicly known by the action of MGI.

7.3.2 In consideration of the license granted hereunder on the Patents, MGI shall pay to HHC or HHC'S nominee a royalty of *** on all Net Sales until expiration of all said Patents, on a country-by-country basis.

7.3.3 In consideration of the license granted hereunder on the Trademark, MGI shall pay to HHC a royalty of *** on all Net Sales throughout the term of this Agreement.

7.3.4 Royalties due by MGI pursuant to this Article shall accrue in United States Dollars (with regard to sales in the United States of America) and in Canadian Dollars (with regard to sales in Canada) and payments shall be made by wire transfer of immediately available funds to an account designated

in writing by HHC in United States Dollars (or in Canadian Dollars, as applicable) within 30 (thirty) days after the end of each Accounting Period, in respect of the Net Sales achieved in that Accounting Period, without prejudice to HHC's right to be paid in accordance with the provisions hereof as well as to any other remedy which may be available to HHC in accordance with this Agreement and/or applicable law, late payments shall bear interests at the prime rate applicable in Switzerland as of the date such payment was originally due.

7.3.5 For the purpose of computing the volume of the Net Sales, the Products shall be deemed to have been sold by MGI or its Affiliates as mentioned at Article 2.8 hereabove on the date of invoicing or on the date of delivering, whichever is first to

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occur, the same to the customer by MGI or its Affiliates, and no deduction shall be made for bad or doubtful debts arising in connection therewith.

7.3.6 ***

7.3.7 MGI will add value Added Tax (VAT) if any. as and where provided by law, to all the royalty accounts rendered and pay such VAT directly to the competent authorities under its own responsibility, or, where so provided by law, mark the royalty accounts

with the notice: "VAT Zero rated", staring the title of the exemption or exclusion.

7.3.8 If any official authorization shall be required to enable MGI to effect any payments of compensations due and payable hereunder, MGI shall use its best efforts to secure such authorization within the times stipulated in this Article, and in the event that by reason of such authorization not having been granted the payment is delayed beyond the times so stipulated. MGI shall so advise HHC and shall effect payment by any other lawful mans indicated by HHC; failing such indications, MGI shall effect payment within 15 (fifteen) days of such authorization being granted.

7.4 All payments to be made pursuant to this Agreement represent actual amounts that HHC is entitled to receive and shall not be subject to any deduction for any reason whatsoever. In the event that such payments become subject to duties, taxes or charges of whatever kind or nature (excluding taxes on HHC's income), such payments shall be increased to such an extent as to allow HHC to receive the net amounts due under this Agreement.

7.5 MGI shall in no case be entitled to off set or otherwise withhold any payment due to HHC hereunder in view of possible, justified or unjustified, claims against HHC.

7.6 If there exists a tax treaty to avoid double taxation between Switzerland and the Territory which reduces the standard rate of withholding tax. MGI shall assist HHC in obtaining the

the Securities and Exchange Commission pursuant to Rule 24b-2 of the Securities Exchange Act of 1954.

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necessary exemption of the withholding tax according to such treaty. Upon submission by HHC of adequate exemption forms or equivalent, if required, MGI shall deduct only Such reduced withholding tax from its payments to HHC and shall submit to HHC the corresponding receipts so that HHC may collect these amounts from its own tax authorities as a tax credit.

ARTICLE 8 - MARKETING AND SALE OF PRODUCTS

8.1 MGI hereby undertakes that it will launch the Products in the Field onto the whole market of each country of the Territory as soon as possible and in any case no later than *** from respective Registration and availability of the necessary commercial supply, and that it shall promptly communicate in writing the relevant launching dates to HHC.

8.2 MGI shall be entitled to resell the Products to its customers in the Territory at such prices as it may determine subject to all applicable laws of the Territory. MGI shall keep HHC fully and timely informed on the price of the Products in the Territory and shall promptly notify any change thereof.

8.3 MGI hereby undertakes and warrants that it shall distribute, promote, market and sell the Products throughout the Territory under its corporate name and responsibility and at its own expense. MGI also undertakes and warrants that distribution, promotion, marketing and sale of the Products in the Territory shall fully comply with all laws, regulations

and requirements at any time being in force in the Territory and shall be fully consistent with the conditions and requirements of the Registration.

8.4 Marketing, advertising and promotional materials concerning the Products and training manuals for MGI's medical representatives shall be developed and prepared by MGI at its own expense and in coordination with HHC, which shall render reasonable assistance in this respect. HHC shall have the right to review and approve the final draft of any said material in advance of print thereof, for the purpose of ensuring compliance of said materials with the international profile and marketing strategy of the Product and the compound, provided that approval by HHC shall he deemed to have been given if HHC does not otherwise respond within ten working days in Switzerland of receipt of such materials.

8.5 MGI shall promote and distribute the Products in accordance with the Product profile and positioning reviewed with HHC end shall regularly supply HHC not later than September

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30 in each year throughout the term of this Agreement with its marketing and promotion plans which shall be discussed in good faith with HHC and shall have to be approved in writing by HHC, which approval shall not be unreasonably withheld or delayed. A marketing

strategy for the Products shall be developed and prepared by MGI consistent with the Registration and with the international profile of the Products as established by HHC. MGI shall keep HHC informed on all its promotional and marketing activities in the Territory regarding the Products and periodic meetings shall be organized between the Parties in order to discuss any and all aspects relevant to the promotion and marketing of the Products in The Territory.

8.6 MGI shall promptly supply HHC free of charge with on copies, in accordance with HHC's reasonable requests, of all marketing, advertising and promotional materials relevant to the Products and of the training manuals for its medical representatives and subject to Article 14.5, HHC shall be free to use, directly or indirectly, any such material for its business inside the Field outside the Territory. In no event shall HHC have the right to use such material in the Territory whether inside or outside the Field.

8.7 MGI undertakes to fully develop and pursue the market for the Product in the Field throughout the Territory. Throughout the term of this Agreement, MGI shall, at its own expense, maintain an active sales organization for marketing and selling the Products in the Field throughout the Territory, maintain an adequate and representative stock of the Products to meet market demand in the Territory and undertakes to effectively distribute, advertise, market, sell and promote the sale and use of the Products in the Field throughout the Territory. ***.

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the Securities and Exchange Commission pursuant to Rule 24b-2 of the Securities Exchange Act of 1934.

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8.8 MGI shall, within September 30th in each year throughout the term of this Agreement, provide HHC with an annual sales forecast in units for each of the Products. It is also agreed that MGI shall develop and supply HHC with sales forecast for 3 (three) years, starting from the date of Registration and revised annually.

8.9 MGI shall make clear in all dealings with its customers and prospective customers that it is acting as licensee and distributor of the Products and not as agent of HHC.

8.10 The final package of the Products, as well as any change thereof, shall be discussed in good faith and mutually agreed by the Parties and shall comply with all requirements of applicable Regulatory Authorities.

8.11 All packaging, insert, sheets labels, advertising and other materials relevant to the Products shall bear the notice "Distributed under license from Helsinn Healthcare SA, Switzerland in such form and manner as HHC may deem appropriate subject to any applicable regulatory requirements in the territory.

ARTICLE 9 - RECORDS AND REPORTS

9.1 MGI shall submit to MGI together with each royalty payment a written royalty statement signed by a responsible officer of MGI which shall show the units of Products sold or otherwise disposed of by MGI, the unit price, the gross sales and the Net Sales of each of the Products, its stock of Products, the quantity of

distributed free medical samples, a detailed listing and appropriate evidence and rationale of any and all discounts granted for each client, wholesaler and/or distributor and any other relevant information in sufficient detail to permit to HHC to determine and verify the royalties due to HHC. Throughout the term of this Agreement and for a period of at least 3 (three) years thereafter, MGI shall keep complete and accurate books, records and accounts in accordance with sound accounting practice covering all its operations hereunder as necessary to determine and verify the units of Products sold or otherwise disposed of by MGI, the gross sales and the Net Sales and the amount of royalties due to HHC. HHC shall have the right, at any time throughout the term of this Agreement and for a period of three years thereafter, during normal business hours and soon at least three (3) business days advance notice, to have such books, records and accounts inspected and audited by its duly authorized representatives or, at HHC'S discretion, by an independent certified public accountant to be nominated by HHC and reasonably acceptable to MGI. MGI shall fully co-operate with HHC, its authorized representatives or independent certified public accountant and make available all work

papers and other information reasonably requested in connection herewith. In the event the inspection or audit reveals that MGI's reports are not in accordance with actual sales and that an underpayment has occurred, MGI shall immediately pay to HHC any underpaid royalties within 10 (ten) days of the date HHC delivers to MGI the relevant inspection or audit report. In case of an underpayment of at least five

percent (5%) of the amounts owing during the audited period, MGI shall also bear all the costs of the inspection or audit and any overdue amounts hereunder shall bear interest at the prime rate applicable in Switzerland as of the date such payment was originally due.

9.2 Within 10 (ten) working days in the United States of America from the end of each month throughout the term of this Agreement, MGI shall supply HHC with a written report showing the units of Products sold and the units of free medical samples distributed during such month in the Territory.

9.3 MGI shall promptly provide HHC with written reports of any importation or sale of any pharmaceutical preparation containing the Compound in the Territory of which MGI has knowledge from any source other than HHC, as well as with any other Information which HHC may reasonably request in order to be updated on the market conditions in the Territory.

ARTICLE 10 - REPRESENTATIONS AND WARRANTIES

10.1 HHC hereby represents and warrants to MGI as follows:

10.1.1 HHC has been duly organized and is validly existing as a corporation in good standing under the laws of Switzerland. HHC has the corporate power and authority to enter into this Agreement and to consummate the transactions contemplated by this Agreement.

10.1.2 The execution delivery and performance of this Agreement, and the consummation of the transactions contemplated by this Agreement, by

HHC have been duly and validly authorized by all requisite corporate actions. This Agreement constitutes a legal, valid and binding agreement of HHC enforceable against HHC in accordance with its terms.

10.1.3 The execution, delivery and performance by HHC of this Agreement requires no action by or in respect of, or consent or approval of, or filing with, any Governmental Authority.

10.1.4 The execution. delivery and performance by HHC of the contemplated transactions do not and will net (A) contravene or conflict with the charter or bylaws f HHC. as applicable, (B) contravene or conflict with or constitute a violation of any provisions of any applicable law binding upon HHC, or (C) constitute a default in any material respect under or give rise so any right of termination, cancellation or acceleration of, or to a loss of any material benefit to which HHC is entitled.

10.1.5 There is no action, suit, investigation or proceeding pending against, or to the knowledge of HHC, threatened against or affecting, HHC before any court, arbitrator or any governmental authority, including but not limited to Regulatory authorities, that in any manner challenges or seeks to prevent, enjoin, alter or materially delay the contemplated transactions, and, to the knowledge of HHC, there is no reasonably valid basis for any such action, suit investigation or proceeding to be brought.

10.1.6 The persons executing this Agreement on behalf of HHC are duly authorized to do so and by so

doing have bound HHC to the terms and conditions of this Agreement.

10.1.7 HHC has received no notice from any of third party licensors that it is in material breach of any of its obligations under the Syntex Agreement, and it is not aware of any material breach of the Syntex Agreement. The Syntex Agreement constitutes a legal, valid and binding agreement of HHC, enforceable against HHC in accordance with its terms.

10.1.8 HHC has licensed sufficient rights to The Parents and Know-how order the Syntex Agreement and, other than the grant of license to third party manufacturers, HHC has not assigned and/or granted licenses to the Patents or Know-how in the Territory for the Field, or entered into any inconsistent prior obligations, to any other person or entity that would restrict or impair the rights granted hereunder to MGI.

10.1.9 To the actual knowledge of HHC, (i) as of the Effective Date hereof the Patents are valid and in full force and (ii) as of the Effective Date hereof it is not aware of any existing or pending patents of third parties which would be infringed by the marketing and sale of the Products in the Field in the territory in accordance with all terms and conditions of this Agreement.

10.1.10 None of the materials provided to MGI pursuant to its due diligence requests contained any untrue statement of material fact.

10.2 MGI hereby represents and warrants to HHC that:

10.2.1 MGI is a corporation duly incorporated, validly existing and good standing under the laws of the state of its incorporation and has all corporate powers and all governmental licenses, authorizations, consents and approvals required to carry on its business as low conducted and as contemplated to be conducted in connection with the transactions contemplated by this Agreement (the "contemplated Transactions"). MGI is duly qualified to do business as a foreign corporation in each jurisdiction where the character of the property owned or leased by it or the nature of its activities (after giving effect to the Contemplated Transactions) make such qualification necessary to carry on its business except where the failure to so qualify would not have a material adverse effect on MGI.

10.2.2 The execution, delivery and performance by MGI of this Agreement and the consummation by MGI of the Contemplated Transactions are within the corporate powers of MGI, and have been duly authorized by all necessary corporate action on the part of MGI. Each of this Agreement and the Escrow Agreement constitutes a legal, valid and binding agreement of MGI, enforceable against MGI in accordance with its terms.

10.2.3 The execution, delivery and performance by MGI of this Agreement requires no action by or in respect of, or consent or approval of. or filing with, any Governmental Authority. other than filings with the SEC in fulfillment of MGI's disclosure obligations under U.S. securities laws.

10.2.4 The execution, delivery and performance by MGI of the Contemplated transactions do not and will not (A) contravene or conflict with the charter or bylaws of MGI, as applicable, (B) contravene or conflict with or constitute a violation of any provisions of any Applicable Law binding upon MGI or (C) constitute a default in any material respect under or give rise to any right of termination, cancellation or acceleration of any agreement or instrument to which MGI is a party, or to a loss of any material benefit to which MGI is entitled.

10.2.5 There is no action, suit, investigation or proceeding pending against, or to the knowledge of MGI, threatened against or affecting, MGI before any court, arbitrator or any governmental authority, including but not limited to Regulatory Authorities, that in any manner challenges or seeks to prevent, enjoin, alter or materially delay

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the Contemplated Transactions, and, to the knowledge of MGI, there is no reasonably valid basis for any such action, suit investigation or proceeding to be brought.

10.2.6 As of February 28, 2001, the authorized capital stock of MGI consists of 30,000,000 shares of common stock and 10,000,000 shares of preferred stock. As of February 28, 2001, (i) 15,538,545 shares of MGI's common stock are issued and outstanding, (ii) no shares of MGI's common stock are issued and held in the treasury of MGI and (iii) 4,075,749 shares of MGI's common stock are reserved for issuance upon exercise of options, warrants, convertible securities or any other right to acquire shares of common stock. There are no shares of preferred stock outstanding or

reserved for issuance upon exercise or conversion of options. The common stock to be issued to HHC in accordance with the terms of this Agreement, if, any, will be, when so issued, duly authorized, validly issued and outstanding and fully paid and non-assessable such shares of common stock shall be freely tradable by HHC and shall not be subject to any preemptive rights.

10.2.7 MGI has heretofore delivered to HHC MGI's Form 10-K for the year ended December 31, 2000 ("10-K") and each and every report filed with the United States Securities and Exchange Commission ("SEC") since the date thereof. As of its date, except for any information corrected or superseded by subsequent filings with the SEC, such reports did not contain any untrue statement of material fact or omit to state a material fact required to be stated therein or necessary to make the statements therein, in light of the circumstances under which they were made, not misleading. The audited consolidated financial statements of not and its subsidiaries, and the notes thereto included in the 10-K have been prepared in accordance with GAAP and present fairly the consolidated financial position of MGI and its subsidiaries as of the date thereof and the results of their consolidated operations and changes in consolidated financial position for the periods then ended. The unaudited consolidated financial statements included in MGI's 2000 quarterly reports filed on Form 10-Q ("10-Q") comply as to form in all material respects with the published rules and regulations of the SEC with respect thereto; and such unaudited financial statements are fairly presented in conformity with generally accepted accounting principles (except as permitted by form 10-Q) applied on a basis

substantially consistent with that of the audited financial

statements included in the 10-K. subject to normal year-end adjustments. Except as and to the extent reflected or reserved against in the balance sheet included in the 10-K or 10-Qs, in the notes thereto or as covered by valid and collectible insurance or other collectible claim for reimbursement, except as set forth in a schedule referred to in this Agreement or in a press release issued by MGI since the filing of the most recent 10-0, there has been no material adverse change in the business, properties on financial condition of MGI and its subsidiaries taken as a whole.

10.2.8 The persons executing this Agreement on behalf of MGI are duly authorized to do so and by so doing have bound MGI to the terms and conditions of this Agreement.

10.2.9 MGI understands and acknowledges that, as of the Effective Data hereof, there is no assurance that there is or will be a market for the Products, and MGI expressly assumes the risk that the Products will be commercially marketable. HHC shall have no liability to MGI of any kind, nor shall MGI be entitled to a return or a refund of any portion of the payments specified at Article 7 hereof if, for any reason, the Registration is not granted in any part or the whole of the Territory or a commercial market does not develop for the Product.

10.2.10 MGI has been given full and complete access to such information and records of HHC as it deemed appropriate to conduct due diligence and such

due diligence has been performed to she full satisfaction of MGI.

ARTICLE 11 - LIABILITIES, INDEMNITIES AND INSURANCE

11.1 MGI shall be fully liable for and shall defend, indemnify and hold HHC and its Affiliates, officers, directors and employees wholly free and harmless from and against any and all liabilities, damages, losses, costs, taxes, expenses (including reasonable attorneys' fees and other expenses of litigation and arbitration), claims, demands, suits, penalties, judgements or administrative and judicial orders arising out of or resulting from any claim, suit or proceeding to the extent arising out of or resulting from (a) the use of the Know-how, the Trademark and the Patent in the Territory by MGI (except to the extent provides in Article 11.2 below); (b) any failure by MGI, its local distributors or Affiliates to comply with any applicable laws, regulations and/or administrative decision regarding the Registration and/or the Products; (c) the performance by MGI of its obligations as HHC's FDA Agent and/or the management and performance by MGI of the post-registration activities connected with the NDA for the Products, as described at Article 4.5 above: (d) the

performance by MGI or its agents of the development work relevant to the products as described at Article 5.3 above; (e) any defect in the results of the development work carried out by or on behalf of MGI as provided at Article 5.3 above; (f) the storage, distribution, sampling, record-keeping, analysis, transfer or sale of the Products by MGI or its agents; (g) the

promotion, advertising and marketing of the Products by MGI or its Affiliates; (h) misuse of the Know-how received hereunder by MGI or its agents; (i) failure of any Products supplied hereunder to comply with the applicable approved specifications in the event that such non compliance (l) could have been detected by MGI carrying out visual inspection on the supplied Products with ordinary diligence or (7) results from any Products which has been altered, changed, packed or re-packed, processed or otherwise treated other than in strict accordance with HHC's instructions and specifications; or (i) any negligent or wrongful act or omission and/or any breach by MGI or by any of its local distributors and/or Affiliates of any of MGI's obligations, representations and/or warranties hereunder.

11.2 HHC shall be liable for and shall defend, indemnify and hold MGI and its Affiliates, officers, directors and employees free and harmless from and against any and all liabilities, damages, losses, costs, expenses (including reasonable attorneys' fees and other expenses of litigation and arbitration), claims, demands. suits, penalties, judgements or administrative and judicial orders, but in no event in excess of the sums already paid by MGI under Article 7 hereabove, arising out of or in any way resulting from any claim, suit or proceeding to the extent arising out of or resulting from (a) a claim that the use of the Know-how and the Patent infringes any intellectual property right of any third party (but only to the extent HHC is covered by Syntex in this regard pursuant to the applicable provisions of the Syntex Agreement); (b) any failure by HHC or its Affiliates to comply with any applicable laws, regulations and/or administrative decision regarding the Registration and/or the Products; (c) the performance by HHC or its agents of

any development activities relating to the Products, as described at Article 4.2 above; (d) any defect in the results of the development work carried out by or on behalf of HHC as provided at Article 4.2 above; (e) the storage, distribution, sampling, record-keeping, analysis, transfer or sale of the Products by MC or its agents; (f) the promotion, advertising and marketing of the Products by HHC or its Affiliates' (g) misuse of the Know-how by HHC or its Affiliates; or (h) any negligent or wrongful act or omission and/or breach by HHC or its Affiliates of any of its obligations and/or warranties hereunder.

11.3 Being understood that each of the Parties hereto shall take all reasonable steps to avoid or mitigate any loss,. damage or liability which might give rise to a claim under this Agreement, a Party seeking indemnification pursuant to this Article 11 (an "Indemnified Party") shall give prompt and full written notice to the Party from whom such

indemnification is sought (the "Indemnifying Party") of the assertion of any claim or the commencement of any action, suit or proceeding in respect of which indemnity is or may be sought hereunder, provided however that no failure to give such notice or co-operation shall relieve the indemnifying Party of any liability and/or obligation hereunder (except to the extent the Indemnifying Party has suffered actual prejudice thereby). The Indemnifying Party shall have the sole right to control the defense and settlement thereof. The Indemnified Party will give the Indemnifying Party such information with respect thereto as the Indemnifying Party may reasonably

request and will co-operate with the Indemnifying Party in the defense of said claim, suit or proceeding as the Indemnifying Party may reasonably request. The Indemnified Party shall not, except at its own cost, voluntarily make any payment or incur any expense with respect to any claim, suit or proceeding without the prior written consent of the Indemnifying Party.

In addition, the Indemnifying Party shall be subrogated to the rights of the Indemnified Party against any third party, and such Indemnified Party hereby assigns to the Indemnifying Party all claims, causes of action and other rights which the Indemnified Party may then have against any third party, including Affiliates and in the case of HHC, against any contract manufacturer of the Products, with respect to the claim, suit or proceeding which is the subject of the claim for indemnification hereunder, conversely, and without in any way limiting the obligation of either Party to indemnify the other Party as herein provided, to the extent that either Party shall fail to perform its indemnification obligations under this Article 11, such Party owing a duty or indemnification hereby assigns to the other Party all claims, cause of action and other rights which the Party Owing such duty may then have against any third party, including Affiliates and, in the case of HHC, against any contract manufacturer of the Products, with respect to the claim, suit or proceeding.

It is understood and agreed that the operation and application of this Article 11.3 are however subject to any right of Syntex (U.S.A.) Inc. under articles 8.3. 8.4 and 8.5 of the Syntex Agreement, which are hereby acknowledged and accepted by MGI.

11.4 MGI shall be solely responsible towards its customers for handling all matters concerning the Products subject to cooperation with HHC on any recall or other regulatory matters that may be injurious to HHC. MGI shall be responsible for any expired Products, whether stored by MGI and/or its local distributors or returned by wholesalers, pharmacists, doctors, hospitals to whom said Products have been sold. MGI shall indemnify, defend and hold HHC and its Affiliates, directors, officers and employees wholly free and harmless from and against any and all liabilities, damages, losses, costs, expenses (including reasonable

attorneys' fees and other expenses of litigation and arbitration) claims, demands, suits, penalties, judgements or administrative and judicial orders arising therefrom; except with respect to any recall or other regulatory action arising from any breach by HHC or its Affiliates of any warranty, representation or other material obligation contained in this Agreement or the negligence or willful misconduct of HHC or its Affiliates.

11.5 Each Party shall indemnify and hold the other Party wholly harmless from and against any and all liabilities, damages, losses, costs, expenses (including reasonable attorneys' fees and other expenses of litigation and arbitration), claims, demands, suits, penalties, judgements or administrative and judicial orders arising out of any behavior contrary or in excess to the provisions of Article 18.1 hereunder.

11.6 THE SOLE REPRESENTATIONS AND WARRANTIES THAT HHC MAKES WITH

RESPECT TO THE MATTER CONTEMPLATED BY THIS AGREEMENT ARE EXPRESSLY SET FORTH IN ARTICLE 10.1. WITHOUT LIMITIMG THE GENERALITY OF THE FOREGOING, HHC MAKES NO REPRESENTATION OR WARRANTY OF ANY KIND, EXPRESS OR IMPLIED, OF MARKETABILITY, CAPACITY OR FITNESS FOR A PARTICULAR PURPOSE WITH RESPECT TO THE KNOW-HOW, THE PATENTS AND/OR THE PRODUCTS. NO ORAL OR WRITTEN REPRESENTATION BY OR ON BEHALF OF HHC SHALL BE INTERPRETED TO CONTAIN ANY SUCH WARRANTY. NEITHER MGI NOR ANY OF ITS EMPLOYEES OR REPRESENTATIVES IS AUIHORISED TO GIVE ANY WARRANTIES OR MARC ANY REPRESENTATION ON BEHALF OF HHC.

11.7 THE SOLE REPRESENTATIONS AND WARRANTIES THAI' MGI MAKES WITH RESPECT TO THE MATTER CONTEMPLATED BY THIS AGREEMENT ARE EXPRESSLY SET FORTH IN ARTICLE 10.2 AND MGI HEREBY DISCLAIMS ALL OTHER REPRESENTATIONS OR WARRANTIES OF ANY KIND, EXPRESS OR IMPLIED. NO ORAL OR WRITTEN REPRESENTATION BY OR ON BEHALF OF MGI SHALL BE INTERPRETED TO CONTAIN ANY SUCH WARRANTY. NEITHER HHC NOR ANY OF ITS EMPLOYEES OR REPRESENTATIVES IS AUTHORISED TO GIVE ANY WARRANTIES OR MAKE ANY REPRESENTATION ON BEHALE OF MGI.

11.8 NOTWITHSTANDING ANY OTHER PROVISION OF THIS AGREEMENT, NEITHER OF THE PARTIES SHALL BE LIABLE TOWARDS THE OTHER FOR INDIRECT, SPECIAL, PUNITIVE,

EXEMPLARY, INCIDENTAL OR CONSEQUENTIAL DAMAGES, INCLUDING WITHOUT LIMITATION LOSS OF PROFITS OR

REVENUES, REGARDLESS OF WHETHER SUCH DAMAGES WERE FORESEEABLE OR NOT. THIS CLAUSE WILL HOWEVER NOT BE APPLICABLE IN CASE OF BREACH BY MGI OF THE LIMITATIONS OF GRANTS AND THE NON-COMPETITION OBLIGATIONS STATED AT ARTICLE 2 AND BREACH BY EITHER PARTY OF THE CONFIDENTIALITY AND NON-USE OBLIGATIONS STATED AT ARTICLE 14 OF THIS AGREEMENT.

11.9 Each Party agrees to procure and maintain in full force and effect during the term of this Agreement valid and collectible insurance policies in connection with its activities as contemplated herein. In particular, MGI at its own cost shall cause HHC and their respective employees, officers, directors and contractors to be added as additional named insured throughout the term of this Agreement on all policies of general commercial liability insurance and product liability insurance covering MGI, which coverage shall, when MGI either initiates clinical trials on the Products or begins marketing or distributing the Products for commercial sale or for promotional purposes, have limits of liability which are commercially reasonable in the Territory but shall be not less than *** per loss occurrence. Within 5 (five) days of the Effective Date and of each beginning of each policy period, MGI shall provide HHC with a certificate evidencing the coverage required hereby and the

amount thereof. Such coverage shall be with a reputable insurance company having at least an A.M. Best "A" rating and shall have to be maintained for not less than 6 (six) years following expiration or termination of this Agreement for any reason or if such coverage is of the "claims made" type, for ten years following expiration or termination of this Agreement for any reason.

ARTICLE 12 - THE PATENTS

12.1 MGI agrees that any Products distributed, promoted, marketed and sold by it will be marked with a notice of patent rights as necessary or desirable under applicable law to enable the Patent to be enforced to the maximum degree.

12.2 MGI shall cooperate with HHC as may be reasonably requested by HHC and at HHC's expense for the purpose of filing for and obtaining patent extensions and supplementary or complementary protection certificates, if available, of the Patents under the relevant applicable laws of each country of the Territory.

12.3 HHC hereby undertakes that it shall use commercially reasonable efforts to cause Syntex to comply with its obligations under the Syntex Agreement with regard to maintenance.

*** Denotes confidential information that has been omitted from the exhibit and filed separately, accompanied by a confidential treatment request, with the Securities and Exchange Commission pursuant to Rule 24b-2 of the Securities Exchange Act of 1934.

defense and enforcement of the Patents in the Territory. In the event that Syntex fails to maintain, defend and enforce such Patents, then HHC shall use commercially reasonable efforts do so, to the fullest extent permissible under the relevant provisions of the Syntex Agreement.

12.4 MGI shall promptly inform HHC in writing upon its becoming aware of any possible third party infringement of the Patents. HHC shall thereafter promptly report the case to Syntex in accordance with the relevant Provisions of the Syntex Agreement, for appropriate action by Syntex and/or HHC. MGI shall provide assistance, bearing exclusively its well costs, as may be reasonably requested by HHC.

12.5 MGI shall promptly inform HHC in writing upon its becoming aware of any notice or claim that the distribution, promotion, marketing and sale of the Product in the Territory for the Field in accordance with the terms and conditions of this Agreement infringe any third party's patent rights, or in the event of the commencement of any suit or action for infringement of any such third party's rights. HHC shall therefore promptly report the case to Syntex in accordance with the relevant provisions of the Syntex Agreement, for appropriate action. MGI shall not settle or compromise any such suit or action without the prior written consent of HHC and shall provide assistance, bearing exclusively its own internal costs, as may be reasonably requested by HHC.

12.6 MGI shall fully co-operate with HHC in connection with any action or proceeding relating to the validity of the Patent, including if required being joined as a necessary party to such action or proceeding at HHC's expense.

ARTICLE 13 - THE SYNTEX AGREEMENT

13.1 MGI acknowledges and understands that the rights granted to it by HHC in this Agreement derive from the Syntex Agreement and are subject to the terms thereof, a copy of which with economic terms redacted MGI has reviewed. The Parties hereby acknowledge and agree that in case of any discrepancy or conflict between this Agreement and the Syntex Agreement, this Agreement shall be construed in a manner consistent with the Syntex Agreement, except for those obligations of HHC towards Syntex which do not have a material impact on MGI's obligations hereunder.

13.2 During the term of this Agreement, HHC agrees to comply in all material respects with its obligations under the Syntex Agreement to the extent necessary to preserve its rights in the Territory thereunder, except to the extent that such compliance is dependent upon MGI.

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13.3 During the term of this Agreement, MCI agrees to act in compliance with the Syntex Agreement to the extent required by the Syntex Agreement, including without limitation any confidentiality restrictions contained therein.

13.4 MGI acknowledges and agrees that HHC has acquired certain rights in and to the Compound pursuant to the Syntex Agreement and that any and all rights that MGI is acquiring pursuant to this Agreement are subject to, in all cases, the Syntex Agreement. Further, MGI acknowledges that under certain circumstances, Syntex has the right to

terminate certain of HHC's rights under the Syntex Agreement. HHC shall promptly provide MGI with a copy of any notice of termination it may receive from Syntex under the Syntex Agreement and the Parties shall thereafter discuss in good faith appropriate steps to cure such termination event.

ARTICLE 14 - CONFIDENTIALITY

14.1 MGI shall treat as strictly confidential, and shall solely for the purpose of and in accordance with this Agreement, the Know-how, Improvements and/or any information and/or document received hereunder or in connection with the Contemplated Transaction not generally known to the trade, including but not limited to non-public information relating to the Patent as well as the results of the development work performed hereunder (all hereinafter referred to as the "Confidential Information"). MGI shall not make such confidential information available to arty third Party, including any of its Affiliates, except to competent government agencies to which it will be necessary to disclose such information, and in this case (a) strictly to the extent requested by said agencies and (b) only upon exercise of its best efforts to cause said agencies to maintain confidentiality thereof.

14.2 Such confidential information shall only be made available to such employees of MGI who are directly and necessarily involved in the authorized use of Confidential Information and who are subject to a secrecy obligation by contract, to the extent strictly necessary to perform their duties and obligations hereunder.

14.3 Notwithstanding expiration or termination of this Agreement for any reason, these confidentiality and non-use obligations shall continue until the

confidential information has become generally known to the public, provided however that nothing contained herein shall in any way restrict or impair the right of MGI to use, disclose or otherwise deal with information which MGI can demonstrate to HHC by clearly convincing documentation:

14.3.1 is or hereafter becomes part of the public domain through no act or omission of MGI, its employees, Affiliates and/or local distributors, or

14.3.2 MGI was in lawful possession of prior to receipt of the confidential information from HHC, or

14.3.3 previously was, or at any time hereafter is, received in good faith by MGI from sources other than HHC and which did not originate, directly or indirectly, from syntax, or

14.3.4 at the time of disclosure, was known by MGI or an Affiliate or local distributor. or after disclosure has independently developed by MGI, an Affiliate or local distributor without use of the Confidential Information.

14.4 Prior to the publication or presentation of any information or data arising from the activities described at Article 5.3 above, MGI shall submit to HHC a summary of the proposed publication or presentation prior to the submission thereof for publication or presentation. The purposes for such prior submission arc: (i) to provide HHC with the opportunity to review and comment on the contents of the proposed publication or presentation, (ii) to identify any Confidential Information to be deleted from the proposed publication or presentation, and (iii)

to agree in good faith on the contents and timing of such proposed publication or presentation.

14.5 HHC shall keep strictly confidential, in the same way mutatis mutandis as provided here above for term in respect of confidential information, any MGI Confidential Information (as defined herein) received from MGI hereunder, except as otherwise specifically provided in this Agreement. As used herein. the term "Confidential Information" shall mean all information disclosed by MGI to HHC, relating to the markets, customers, suppliers, patents or patent applications, inventions, know-how, data or information, products, research and development, procedures, designs, formulas, business plans, financial projections, employees, consultants or any other similar aspects MGI's present or future business, whether such information is disclosed in written, oral, electronic, graphic or other format.

ARTICLE 15 - FORCE MAJEURE

15.1 If the performance of this Agreement is prevented or restricted by government action, war, fire, explosion, flood, strike, lockout, embargo, act of God, or any other similar cause

beyond the control of the defaulting Party, the Party so affected shall be released for the duration of the force majeure, or such other period agreed between the Parties as being reasonable in all circumstances, from its contractual obligations directly affected by the force majeure, provided that the Party concerned shall:

15.1.1 give prompt notice in writing to the other Party of the cause of force majeure;

15.1.2 use commercially reasonable efforts to avoid or remove such cause of non-performance;

15.1.3 continue the full performance of this Agreement as soon as such cause is removed.

15.2 The Parties shall take all reasonable steps to minimize the effects of force majeure on the performance of this Agreement and shall, if necessary, agree on appropriate measures to be taken. Should the force majeure continue for more than 6 (six) months, then the other Party shall have the right to terminate this Agreement forthwith.

15.3 Notwithstanding anything contained in this Article 15, obligations to pay money accruing prior to the force majeure event are never excused by force majeure.

ARTICLE 16 - TERM

16.1 This Agreement comes into force at the Effective Date hereof, unless terminated earlier pursuant to the provisions hereof and subject to the validity of the Syntex Agreement, it shall remain in force for a period of 10 (ten) years from the date of launching by MGI of the first of the Products and, unless either of the Parties gives notice of Termination to the other Party in writing 6 (six) months before the termination of the initial or of any extension period, it shall be automatically renewed for periods of 3 (three) years.

ARTICLE 17 - TERMINATION

17.1 Each of the Parties reserves the right to terminate this Agreement in case of any substantial or persistent breach of any of the terms and conditions of

this Agreement by the other Party, including, without limitation, as provided at Articles 2.12 and 7.5.6 above. The defaulting Party shall be given in writing a 60 (sixty)-day period, except as otherwise specifically provided, to fulfil its obligations hereunder and, if after such period it is still in breach of

the Agreement, the other Party shall have the right to terminate this Agreement by written notice to the defaulting Party. In addition, MGI hereby acknowledges and agrees that HHC shall be entitled to terminate this Agreement by written notice to MGI in case of termination of any agreement between MGI and any third party for the supply of Products to MGI as per Article 2.5 above due to a breach by MGI.

17.7 Either Party shall have the right to terminate this Agreement upon written notice to the other Party, if such Party shall become insolvent or shall make an assignment for the benefit of creditors or become involved in receivership, bankruptcy or other insolvency or debtor relief proceedings, or any similar proceedings or in proceedings, voluntary or forced, whereby the party involved is limited in the free and unrestrained exercise of its own judgement as to the carrying out of the terms of this Agreement. The Parties intend that upon HHC's termination of this Agreement pursuant to this Article 17.2, all rights granted hereunder to MGI shall be terminated and revert to HHC. The Parties acknowledge and agree that all rights and licenses granted pursuant to this Agreement are, and shall otherwise be deemed to be, for purposes of Article 365(n) of the Bankruptcy Code, licenses of rights to "intellectual property" as defined

under Section 101(52) of the Bankruptcy Code, and that MGI, as a licensee hereunder, shall retain and may fully exercise all of its rights and elections under the Bankruptcy Code.

17.3 In case the ownership or control (as this term is defined at Article 1.2 here above) of MGI or of a legal entity directly or indirectly owning or controlling MGI changes (whether by merger, consolidation, reorganization, take over, change in the ownership of the share capital or otherwise), details of any such change in ownership or control shall be notified in writing by MGI to HHC as soon as possible and in any case no later than 5 (five) days of its occurrence. HHC shall then have the right to terminate this Agreement by giving MGI or the new entity owning or controlling MGI 30 (thirty) days advance notice in writing if (i) the entity owning or controlling MGI has in its portfolio a product competing with the Products (as defined at article 2.4 here above) and/or (ii) MGI's commitments and investments on the Products in terms of promotion and marketing efforts, sales force activities, sales performance etc. are not maintained by said new entity.

17.4 ***

*** Denotes confidential information that has been omitted from the exhibit and filed separately, accompanied by a confidential treatment request, with the Securities and Exchange Commission pursuant to Rule 24b-2 of the Securities Exchange Act of 1934.

17.5 HHC shall have the right to terminate this Agreement by written notice to MGI if MGI fails to

launch the Products as provided in Article 8 hereabove, or if MGI or any of its agents, employees, Affiliates or distributors breaches the confidentiality and/or non use obligations provided for in Article 14 hereabove. MGI shall have the right to terminate this Agreement by written notice to HHC if HHC or any of its agents, employees or Affiliates breaches the confidentiality and/or non use obligations provided for in Article 14.5 hereabove.

17.6 Without limiting the generality of the foregoing, termination or expiration of this Agreement for any reason shall not extinguish any existing claims either of the Parties may have for indemnification and shall not preclude either of the Parties from pursuing any claim for indemnification such Party otherwise may have to the extent that the circumstances giving rise to such claim arose prior to, on or after the date of termination or expiration.

17.7 Upon expiration or termination of this Agreement for any reason, MGI shall:

17.7.1 subject to Article 17.7.4 hereunder, promptly cease any use and/or exploitation of the Registration;

17.7.2 subject to article 17.7.4 hereunder, promptly cease any use of the Trademark and not hold itself out as a distributor of the Products;

17.7.3 subject to Article 17.7.4 hereunder, promptly terminate using the Know-how, the Improvements and the results of the development work carried out in accordance tenth Article 5.3 hereunder and return or deliver all such materials to HHC without retaining copies, notes, summaries or translations thereof;

17.7.4 promptly terminate distributing, promoting, marketing and selling the Products onto the market,

provided that it shall have a three-month period to sell its existing stock of Products, subject to payment of royalties hereunder. Any stuck remaining at the expiry of said three months period shall be destroyed by MGI at MGI's expenses, unless otherwise directed by HHC.

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17.8 Unless otherwise set forth herein, the Parties' remedies under this Agreement are intended to be cumulative and not mutually exclusive.

ARTICLE 18 - MISCELLANEOUS

18.1 Independent contractor status

The status of HHC and MGI under the business arrangement established by this agreement is that of independent contractors. MGI shall perform as an independent contractor in relation to both HHC and MGI's customers and, accordingly, MGI shall purchase the Products from HHC or HHC's nominee and resell them to its customers in its own name and for its own account. With the sole exception of the provisions of article 4.5 here above regarding MGI's role as HHC's FDA Agent, MGI has no authority whatsoever to act as an agent or representative of HHC nor any authority or power to contract in the name of or create any liability against or otherwise bind HHC in any way for any purpose, nor shall HHC have such authority or power to so bind MGI.

18.2 Notices

All reports, notices and communications given or made pursuant to thin Agreement by one Party to the other shall be validly given or made for all purposes, in the absence of acknowledgement of receipt, or the

date of nailing if nailed by registered airmail or by international courier to the addressee Party at the following addresses, respectively:

HELSINN HEALTHCARE SA
P.O. BOX 357
691S Pambio-Moranco
SWITZERLAND
For the attention of the Legal Department

MGI PHARMA INC.
6300 West Old Shakopee Road
Suite 110
Bloomington, MN 55438-7318
USA
For the attention of Manager, Legal Affairs

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with a copy to:

Dorsey & Whitney LLP
220 S. 6th Street
Minneapolis, MN 55402
Attention: Timothy S. Hearn

18.3 Binding Effect. Subject to the provisions of articles 2.1, 2.8 and 18.6 herein, this Agreement shall inure to the benefit of, and be binding upon, the respective successors of the Parties.

18.4 Waiver. The failure of a Party to insist upon strict performance of any of the terms and conditions of this Agreement by the other Party shall not constitute a waiver of any of the provisions hereof and no waiver by a party of any of said terms and conditions shall be deemed to have been made unless expressed in writing and signed by such waiving Party.

18.5 Interpretation.

18.5.1 The language of this Agreement is English. No translation into any other language shall be taken into account in the interpretation of the Agreement itself.

16.5.2 The headings in this Agreement are inserted for convenience only and shall not affect its construction.

18.5.3 Where appropriate, the terms defined in Article 1 hereabove and denoting a singular number only shall include the plural and vice versa.

18.5.4 References to any law, regulation, statute or statutory provision includes a reference to the law, regulation. statute or statutory provision as from time to time amended, extended or re-enacted.

18.6 Assignment. This Agreement and the licenses and other rights conferred upon MGI under this Agreement are personal to MGI and cannot be transferred, sublicensed, assigned or otherwise disposed of (by operation of law or otherwise) by MGI without the prior, written authorization of which authorization shall not be unreasonably withheld; provided, however, that MGI shall be entitled to assign this Agreement without such consent in connection with a merger, acquisition or sale of substantially all of its assets or to any of its Affiliates, in accordance however with the criteria established at Article 17.3 hereabove.

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HHC shall have the right to assign or transfer, in whole or in part, this Agreement to any of its Affiliates.

18.7 Statements to the Public. Neither HHC nor MGI shall make or procure or permit the making of any announcement or statement to the public with respect to This Agreement, its subject matter or any ancillary natter without the prior consent of the other Party, which consent shall not be unreasonably withheld.

The wording and the timing of any press release or of any other announcement and/or statement to the public shall have to be agreed upon in advance between the Parties.

Nothing herein shall prohibit MGI from disclosing information to the extent required by the U.S. securities and Exchange commission, Nasdaq or other similar authorities. It is however understood and agreed that (a) the contents of any copy of this Agreement, or of any other agreement between the Parties, which has to be sent to the SEC shall have to be previously agreed upon between the Parties and shall be in redacted form to maintain The confidentiality of proprietary and/or competitivity sensitive information, and (b) MGI shall use its best efforts to obtain authorization by the SEC to keep confidential any information which is deemed to be confidential by the Parties or any of them or which may, in either Party's opinion, put a competitive advantage to third parties.

18.8 Expenses. Unless specifically and expressly provided for to the contrary in this Agreement, each of the Parties shall bear its own expenses incurred in connection with the performance of this Agreement.

18.9 Survival. The following provisions shall survive expiration or termination of this agreement for any reason: Articles 1 (whole clause), 3.4, 4.2 (last

sentence), 4.7 (last sentence), 9.1, 11 (whole clause), 14 (whole clause), 17.6 through 17.8, 18 (whole clause), 27 (whole clause) and 21 (whole clause).

ARTICLE 19 -APPENDICES

19.1 The following Appendices shall be an integral part of this Agreement:

Appendix 1: List of Know-how Items

Appendix 2: Patents Appendix 3: Products

Appendix 4: Development Chart

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Appendix 5: HHC'S Post-Registration Regulatory Activities

Appendix 6: Adverse Events Reporting

Appendix 7: Products Recall Procedure

Appendix 8: Escrow Agreement

Appendix 9: MGI's unit sales base forecast - Annual Minimum sales

Appendix 10: Promotion and Marketing Activities

ARTICLE 20 - LAW TO GOVERN AND ARBITRATION

20.1 This Agreement shall be governed by and construed in accordance with the law of Switzerland

20.2 It is the express decision of the Parties that any dispute which may arise between the Parties concerning this Agreement, which cannot be settled amicably, shall be submitted to arbitration for final decision. Also, any dispute as to the applicability of the arbitration clause shall be subject to arbitration.

Notwithstanding the above, each Party expressly, reserves the right to seek judicial relief from a court of competent jurisdiction if the other Party is or appears to be in violation of such other Party's obligations of non use and non disclosure under Article 14 above, including, without limitation, any injunction or other preliminary relief.

20.3 It is expressly agreed that arbitration shall be held in English language in Genova (Switzerland), and conducted under the Rules of Arbitration of the international Chamber of Commerce. The court of arbitration shall consist of three arbitrators. Each Party is entitled to nominate one arbitrator. If, within one month after receipt of the request for arbitration filed by one Party, the other has not yet appointed an arbitrator, such arbitrator shall be appointed by the International Court of Arbitration of the international chamber of commerce on request of the first Party. The two arbitrators shall nominate the president of the court of arbitration, who shall be a lawyer qualified to practice and currently practicing as an attorney-at-law or as a judge. If they cannot come to terms within one month, the president of the court of arbitration shall be nominated by the International Court of Arbitration of the International Chamber of Commerce, on request of the more diligent Party.

20.4 If one of the arbitrators is unable to fulfil his/her duties for any reason the Party having nominated him/her shall nominate another arbitrator within one month, otherwise this

arbitrator will be nominated by the International Court of Arbitration of the International Chamber of Commerce.

20.5 If the arbitrators or the president have to be replaced, the proceedings do not have to be started anew and will continue at the point where they were stopped.

20.6 The court of arbitration is hereby expressly instructed to act with most diligence and to keep any term as short as possible and to render the decision as soon as possible.

20.7 The Parties hereby stipulate that any arbitration hereunder shall be subject to the following rules; (a) the arbitrators may not award or assess punitive damages against either Party; and (b) each Party shall bear its own costs and expenses of the arbitration and one-half (1/2) of the fees and costs of the arbitrators, subject to the power of the arbitrators, in their sole discretion, to award all such reasonable costs, expenses and fees to the prevailing Party.

20.8 The Parties agree that the arbitrator's award shall be the sole and exclusive remedy between them regarding any claims, counter-claims, issues or accountings presented or pled to the arbitrator and that any costs, fees or taxes incident to enforcing the award shall be, to the maximum extent permitted by law, charged against the Party resisting such enforcement.

20.9 Notwithstanding the foregoing, any Party may bring a case of action against the other Party before any court of competent jurisdiction at the domicile of the defendant Party, if and to extent that any arbitral award rendered in the arbitration proceedings is unenforceable.

20.10 subject to the provisions of Article 20.9. in the event that an award is rendered pursuant to this Article 20 by an arbitrator in favor of HHC, the Parties acknowledge and agree that such award shall be enforceable by HHC, and MGI hereby consents to the exclusive jurisdiction for purposes of enforcement of any such award against MGI to the United States District Court for the District of Delaware, or, if jurisdiction or venue cannot be laid therein, the jurisdiction of any courts in the state of Delaware. Each of the Parties hereby consents to the exclusive jurisdiction of such courts (and of the appropriate appellate courts) for the purposes set forth above.

ARTICLE 21 - ENTIRETY OF AGREEMENT AND SEVERABILITY

21.1 This Agreement supersedes all prior agreements and understandings, whether oral or written, made by either Party or between the Parties and constitutes the entire agreement of

the Parties with regard to the subject matter hereof. This Agreement shall not be considered extended, cancelled or amended in any respect unless done so in writing and signed on behalf of the Parties hereto.

21.2 The Parties hereby expressly state that it is the intention of neither Party to violate any rule, law and regulations. If any provision of this Agreement is rendered invalid or unenforceable, the Parties agree to renegotiate such provision in good faith and to replace it with valid and enforceable provisions in such a way as to reflect as nearly as possible the intent and purpose of the original provision.

IN WITNESS WHEREOF, the Parties hereto have caused this Agreement in be executed in duplicate by their duly authorized officers.

For and on behalf of
HELSINN HEALTHCARE SA

/s/ Riccardo Braglia
Riccardo Braglia
Managing Director

/s/ Enrico Braglia
Enrico Braglia
Managing Director

For and on behalf of
MGI PHARMA, INC.

/s/ Charles N. Blitzer
Charles N. Blitzer
President and Chief Executive officer

/s/ Leon O. Moulder, Jr.
Leon O. Moulder, Jr.
Executive Vice President

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Exhibit 99.2

Supply and Purchase Agreement between HELSINN BIREX PHARMACEUTICALS LTD and MGI Pharma, INC.

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THIS AGREEMENT (hereinafter called "Agreement") is effective as of this 5th day of April 2001 (hereinafter called "Effective Date"), between HELSINN BIREX PHARMACEUTICALS LTD, a corporation organized and existing under the law of the Republic of Ireland and having its registered office at Damastown, Mulhuddart, Dublin 15, Republic of Ireland (hereinafter called "HBP") of the one part, and MGI PHARMA, INC., a corporation organized and existing under the law of the state of Minnesota, United States of America and having its registered office at 6300 West Old Shakopee Road, Suite 110, Bloomington, MN 55438-2318, USA (hereinafter coiled "MGI"), of the other part.

RECITALS

a. MGI carries on business as a pharmaceutical company and in particular for the purpose of this Agreement, has entered into a License Agreement (as hereinafter defined) with Helsinn Healthcare SA, Via Pian Scairolo, 6912, Pazzallo, Switzerland (hereinafter called "HHC") by means of which MGI has been licensed with the right to distribute, promote. market and sell the Products (as hereinafter defined) in the Territory and has undertaken to purchase the Products exclusively from a source indicated or approved in writing by HHC.

b. HBP carries on business as a pharmaceutical manufacturer and Trader and, in particular for the purpose of this Agreement, represents that it has been duly appointed by HHC as the supplier of the Products to MGI for the purpose of the sale of said Products by MGI.

c. The Parties agree that this preamble constitutes an integral part of this Agreement and all capitalized terms used in this preamble shall have the meaning as defined in Article 1 hereafter.

NOW, THEREFORE, in consideration of the foregoing and of the mutual covenants and conditions herein contained, the Parties hereby agree as follows:

ARTIGLE 1 - DEFINITIONS

The following terms as used in this Agreement have, unless the context clearly

1.1 "Accounting period" means the quarters ending 31st March, 30th June, 30th September and 31st December in each year throughout the term of this Agreement.

1.2 "Affiliate" means an organization that, whether now or in the future, controls, is controlled by or is under common control with a Party. For the purposes of this definition, the terms "controls," "controlled by," and "under common control with" as used with respect to any Party, means the possession (directly or indirectly) of fifty percent or more of the voting stock or other equity interest of a subject entity with the power to vote, or the power in fact to control the management decisions of such entity through the ownership of securities, by contract or otherwise.

1.3 "Compound" means the active pharmaceutical ingredient (3a5-2-[(5)-1-Azabicyclo[2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1H-benz[de]isoquinoline hydrochloride, having the generic name palonosetron hydrochloride (INN) for use in human medicine.

1.4 "FDA" means the U.S. Food and Drug Administration or any successor agency.

1.5 "License Agreement" means the license agreement entered into between MGI and HHC on April 6th, 2001 granting MGI the exclusive right to distribute. market and sell the Products in the Territory.

1.6 "Net Sale Price" means the gross sale price in local currencies of the Products in the Territory by MGI and/or its Affiliates, including any local affiliate in Canada, for arm's lenghth sales to any non-Affiliated third party less those normal and customary deductions made under Generally Accepted Accounting Principles at arrive at Product sales.

*** Denotes confidential information that has been omitted from the exhibit and filed separately, accompanied by a confidential treatment request, with the Securities and Exchange commission pursuant to Rule 24b-2 of the Securities Exchange Act of 1934.

1.7 "Net Sales" means the gross sales in local currencies of all Products sold in the Territory by MGI and/or its Affiliates, including any local Affiliate in Canada, for arm's lenghth sales to any non Affiliated third party less those normal and customary deductions made under Generally Accepted Accounting Principles to arrive at Product sales. ***

*** Denotes confidential information that has been omitted from the exhibit and filed separately, accompanied by a confidential treatment request, with the Securities and Exchange Commission pursuant to Rule 24b-2 of the Securities Exchange Act of 1934.

1.8 "Parties" means HBP and MGI and "Party" means either of them as the context indicates.

1.9 "Products" means the pharmaceutical preparations for human use in I.V. dosage form, containing the Compound as an active ingredient, in the formulation which will be described in the Registration. The current formulation as submitted to the Food and Drug Administration of the United States of America in the IND 39,797 Amendment # 64 and to the Therapeutic Products Programme of Canada in the IND 9427-H0836-21C is described in the First Appendix hereto.

1.10 "Registration" means any official approval, or authorization by the competent regulatory authorities, which is legally, required to lawfully market the Products in the territory, including, without limitation, any governmental price approval or reimbursement approved under a national health insurance system.

1.11 "Syntex Agreement" means a license agreement between HHC and Syntex (U.S.A.) LLC dated 23rd June 1998 by means of which HHC in-licensed world-wide rights on the compound and Products.

1.12 "Territory" means the United States of America and its possessions and territories (Puerto Ricom United Stares Virgin Islands), and canals and its provinces, possessions and territories.

ARTICLE 2 - PURCHASE OF PRODUCTS

2.1 Throughout the term of this Agreement, and subject to the terms and conditions contained herein, MGI undertakes to purchase exclusively from HBP, and HBP undertakes to sell to MGI. MGI's entire requirements of the Products to be distributed, promoted, marketed and sold by MGI or MGI's Affiliates under the License Agreement.

2.2 MGI shall not use the Products for any other purpose than distributing, promoting, marketing and selling said Products in accordance with the terms and conditions of the License Agreement.

ARTICLE 3 - PRICE AND TERMS OF PAYMENT

3.1 The price of the Products purchased by MGI hereunder is as set Forth in the Second Appendix hereto. ***

3.2 Any payment by MGI for the delivered Products shall be effected by wire transfer of immediately available funds to an account designated in writing by HBP in United States Dollars within 30 (thirty) days from the date of receipt of the invoice (which shall be deemed to have been received on the date following the date of delivery to MGI by telefax) and be deemed paid when freely received. MGI shall bear all costs in connection with effecting payments.

3.3 MGI shall in no case be entitled to off set or otherwise withhold any Payment due to HBP in view of possible, justified or unjustified, claims against HBP.

3.4 ***

ARTICLE 4 - FORECASTS. ORDERS AND TERMS OF DELIVERS

4.1 MGI shall, prior to September 30th in each year throughout the term of this Agreement, supply HBP in writing with a purchase forecast for the Products for each Accounting Period of the following calendar year. Any such forecast shall be deemed to be a binding order by MGI for the first Accounting Period ***

*** Denotes confidential information that has been omitted from the exhibit and filed separately, accompanied by a confidential treatment request, with the Securities and Exchange Commission pursuant to Rule 24b-2 of the Securities Exchange Act of 1934.

of such year. Moreover MGI shall issue its firm orders relevant to the three following Accounting Periods at least 90 (ninety) days in advance of the requested delivery date and, at each time, it shall supply HBP with its purchase forecast relevant to a further calendar year so as to maintain at all tines a rolling twelve-month purchase forecast and shall promptly notify HBP of any projected changes thereto.

4.2 The Products will be supplied to MGI only against MGI's written order and all orders shall be subject to written acceptance and confirmation by HBP before becoming binding. Such acceptance and confirmation may be by facsimile or otherwise. Each order by MGI shall be for a minimum quantity corresponding to the size of one production batch of Products, as shall be indicated in due time by HBP, or multiples thereof.

HBP shall use commercially reasonable efforts to execute all orders received and accepted pursuant to this article within 90 (ninety) days from the date of receipt of the relevant order by HBP. MGI's firm Orders shall be at least *** and not more than *** of its forecast of Products for the applicable Accounting Period as per Article 4.1 hereabove. HBP shall not be obliged to supply more than *** of MGI's initial forecast of Products within the applicable Accounting Period. However, in the event that, in any Accounting Period, MGI's orders are more than *** of the relevant forecasts, HBP agrees to use commercially reasonable efforts to supply MGI with amounts in excess of MGI's forecast of Product during said Accounting Period, on condition however that this shall not hamper, delay or otherwise prejudice supplies of Products to any other of HBP's customers. MGI shall keep throughout the term of this Agreement a stock of Products adequate to meet market demand and to cover possible shortages in the supplies of Products, such stock to approximately correspond at least to three-month average sales. In turn, HBP undertakes to keep throughout the term of this Agreement a stock of Products in semi-finished form (i.e. vials without final packaging) approximately corresponding to at least to two-month average sales.

4.3 Any purchase order or acknowledgement thereof, whether printed, stamped, typed or written, shall be governed by the terms and conditions of this Agreement and none of the provisions of such purchase order or acknowledgement thereof shall be applicable, except those specifying quantity

*** Denotes confidential information that has been omitted from the exhibit and filed separately, accompanied by a confidential treatment request, with

the Securities and Exchange Commission pursuant to Rule 24b-2 of the Securities Exchange Act of 1934.

ordered, delivery dates and invoice information, and with respect to those specifications only to the extent that they are in compliance with the terms and conditions of this Agreement. To the extent there is any discrepancy between this Agreement and any purchase order or acknowledgement thereof, this Agreement will control.

4.4 All orders of Products shall be delivered DDU (Incoterms 2000) MGI's or MGI nominee's warehouse in the United States of America, unless otherwise agreed in writing by the Parties. MGI shall be solely responsible for all customs clearance of, and import/ export regulations for, the Products and it shall bear and pay all taxes, duties, levies and other charges imposed by reason of its purchase, import and resale of the Products.

4.5 If, for any reason, HBP is unable to supply MGI's firm orders for the Products up to the forecasted level, or is unable to supply such quantities in a manner meeting the specifications, during any ninety (90) day period, the Parties shall promptly meet to discuss the reasons for such failure to supply, and HBP shall thereafter designate in third party manufacturer to manufacture the Products. HBP shall provide to such third party manufacturer, appropriate manufacturing licenses and reasonable technical assistance to enable it to manufacture the Products, in a manner that minimizes disruption to MGI of Product supply.

ARTICLE 5 - QUALITY

5.1. HBP shall manufacture, or shall cause the Products to be manufactured, in accordance with applicable current mood manufacturing Practice and with applicable specifications.

5.2 Each batch of Products shall be delivered to MGI accompanied by appropriate certificates of analysis, attesting the compliance of each relevant batch with the specifications for said Products as the same are contained in the Registration of the Products. MGI shall carry out appropriate visual inspection of the products, as well as any other analysis which MGI may deem appropriate or necessary, upon receipt. Should it occur that any batch of Products does not meet said approved specifications, MGI shall, as soon as possible and in any case within 30 (thirty) days after receipt of the Products, give notice in writing to HBP specifying in detail the claimed non-conforming characteristics of the Products.

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In the absence of MGI's notification within the said term, MGI shall be deemed to have accepted such Products. Should HBP recognize that such Products delivered to MGI do not meet the approved specifications, and provided MGI demonstrates that the Products have been properly handled and stored after delivery, HBP shall replace, at its own cost, such Products. Such replacement shall be done, to the extent possible, in accordance with the timing reasonably agreed among the Parties which, in any event, shall be as soon as reasonably possible thereafter. It is u derstood and agreed that HBP's

total responsibilities hereunder shall be limited to said replacement of Products. Should HBP not be in agreement with MGI's claim of defect, a sample of the alleged defective Products shall be submitted for analysis to an independent laboratory to be agreed in good faith between MGI and HBP in writing. The decision of such laboratory shall be final and binding for both MGI and HBP and the corresponding expenses will be paid by the Party found to be in error.

5.3 HBP shall at any time be free to determine the manufacturer and the place of manufacture of the Products, subject however to applicable laws and regulations and to compliance with the License Agreement. In no event shall MGI be entitled to manufacture any Products by virtue of this Agreement.

5.4 MGI shall store and distribute, and shall cause the Products to be stored and distributed, according to applicable current Good Manufacturing Practice or any other applicable laws and regulations. MGI shall permit HBP's representatives, during normal business hours and upon three business days advance notice in writing but not more than once a year or as otherwise reasonably requested by HBP, to inspect those areas of the warehouses of MGI, its Affiliates and its distributors where the Products are inspected, analyzed or stored, for the purpose of verifying compliance with applicable laws and regulations as well as with this Agreement. Such inspection shall include, without limitation, the right to examine any relevant internal procedures or records of MGI, its Affiliates and distributers. MGI shall give and shall cause its Affiliates and distributors to give, all necessary assistance for a full and correct carrying out of the inspection by HBP. No such inspection by HBP shall

relieve MGI, its Affiliates and distributors of any of their obligations under this Agreement in any way whatsoever.

5.5 The products shall be supplied by HBP or HBP's nominee to MGI in a secondary package inclusive of leaflet, ready for distribution. Artwork and all necessary films for printing packs, package inserts, leaflets and labels will be

prepared and supplied by MGI, at its expenses, based upon indications, box design anti measurements provided by HBP. Any change shall have to be communicated by MGI to HBP at least 6 (six) months in advance of its enforcement. The costs relevant to the change, including costs relevant to repackaging or disposal of Products in stock at HBP, (i) shall be entirely borne by MGI if the change has been requested by MGI, and (ii) shall be shared between the parties in case the change is required by any regulatory authority or is jointly deemed advisable by the Parties.

5.6 Events concerning Product recall, complaint, field alert or product withdrawal relevant to the Products marketed by MGI in the Territory shall be governed by the procedures and rules established in the Licence Agreement.

ARTICLE 6 - RECORDS AND REPORTS

6.1 MGI shall submit to HBP at the end of each Accounting Period a written statement signed by a responsible officer of MGI which shall show the units of Products sold or otherwise disposed of by MGI, the gross sale price and the Net Sale Price of the Products

and any change thereof, together with a detailed listing and appropriate evidence or any and all discounts granted for each client, wholesaler and/or distributor as necessary to permit to HBP to calculate and verify the supply price of the Products as per the second Appendix hereto, the gross sales and the Net Sales for said Accounting Period and the existing stock of Products in MGI's, its Affiliates' and its distributors' warehouse. Throughout the term of this Agreement and for a period of at least 3 (three) years thereafter, MGI shall keep complete and accurate books, records and accounts in accordance with sound accounting practice covering all its operations hereunder as necessary to determine and verify the units of Products sold or otherwise disposed of by MGI, the Net Sale Price of the products, the Net Sales for each Accounting Period, and any change thereof. HBP shall have the right, at any time throughout the term of this Agreement and for a period of three years thereafter, during normal business hours and upon at least three (3) business days advance notice, to have such books, records and accounts inspected and audited by its duly authorized representatives or, at HBP's discretion, by an independent certified public accountant to be nominated by HBP and reasonably acceptable to MGI. MGI shall fully co-operate with HBP, its authorized representatives or independent certified public accountant and make available all work papers and other information reasonably requested in

connection herewith. In the event the inspection or audit reveals that an underpayment has occurred, MGI shall immediately pay to HBP any underpaid amount within 10 (ten) days of the date HBP delivers

to MGI the relevant inspection or audit report. In case of an underpayment of at least five percent (5%) of the amounts owing during the audited period, MGI shall also bear all the costs of the inspection or audit and any overdue amounts hereunder shall bear interest at the prime rate applicable in Switzerland as of the date such payment was originally due.

6.2 Each of the Parties hereby agrees that any and all communications sent to or received from the other Party hereunder, including but not limited to those described at Article 13.2 hereunder, shall be immediately sent in copy by telefax to HHC.

ARTICLE 7 - REPRESENTATIONS AND WARRANTIES

7.1 HBP hereby represents and warrants to MGI as follows:

7.1.1 HBP has been duly organized and is validly existing as a corporation in good standing under the laws of the Republic of Ireland. HBP has the corporate power and authority to enter into this Agreement and to consummate the transactions contemplated by this Agreement,

7.1.2 The execution, delivery and performance of this Agreement, and the consummation of the transactions contemplated by this Agreement, by HBP have been duly and validly authorized by all requisite corporate actions. This Agreement constitutes a legal, valid and binding agreement of HBP enforceable against HBP in accordance with its terms.

7.1.3 The execution, delivery and performance by HBP of this Agreement requires no action by or in respect of, or consent or approval of, or filing with, any Governmental Authority.

7.1.4 The execution, delivery and performance by HBP of the contemplated transactions do not and will not (A) contravene or conflict with the charter or bylaws of HBP, as applicable, (B) contravene or conflict with or constitute a violation of any provisions of any applicable law binding upon HBP or (C) constitute a default in any material respect under or give rise to any right of termination, cancellation or acceleration of, any

agreement or instrument to which HBP is a party, or to a loss of any material benefit to which HBP is entitled.

7.1.5 There is no action, suit, investigation or proceeding pending against, or to the knowledge of HBP, threatened against or affecting, HBP before any court, arbitrator or any governmental authority, including but not limited to Regulatory Authorities, that in any manner challenges or seeks to prevent, enjoin, alter or materially delay the contemplated transactions, and, to the knowledge of HBP, there is no reasonably valid basis for any such action, suit, investigation or proceeding to be brought.

7.1.6 The persons executing this Agreement on behalf of HBP are duly authorized to do so and by so going have bound HBP to the terms and conditions of this Agreement.

7.1.7 HBP has been duly authorized and entrusted by HHC to supply the Products to MGI.

7.2 MGI hereby represents and warrants to HBP as follows:

7.2.1 MGI is a corporation duly incorporated, validly existing and in good standing under the laws of the state of its incorporation and has all corporate powers and all governmental licenses, authorizations, consents and approvals required to carry on its business as now conducted and as contemplated to be conducted in connection with the transactions contemplated by this Agreement (the "Contemplated Transactions"). MGI is duly qualified to do business as a foreign corporation in each jurisdiction where the character of the property owned or leased by it or the nature of its activities (after giving effect to the Contemplated Transactions) make such qualification necessary to carry on its business, except where the failure to so qualify would not have a material adverse effect on MGI.

7.2.2 The execution, delivery and performance by MGI of this Agreement and the consummation by MGI of the Contemplated Transactions are within the corporate powers of MGI, and have been duly authorized by all necessary corporate action on the part of MGI. This Agreement constitutes a legal, valid and binding agreement of MGI, enforceable against MGI as applicable in accordance with its terms.

7.2.3 The execution, delivery and performance by MGI of this Agreement requires no action by or in respect of, or consent or approval of, or filing with, any Governmental Authority, other than filings with the

SEC in fulfillment of slot's disclosure obligations under U.S. securities laws,

7.2.4 The execution, delivery and performance by MGI of the Contemplated Transactions do not and will not (A) contravene or conflict with the charter or bylaws of MGI, as applicable, (B) contravene or conflict with or constitute a violation of any provisions of any Applicable Law binding upon MGI or (C) constitute a default in any Material respect under or give rise to any night of termination, cancellation or acceleration of, any agreement or instrument to which MGI is a party, or to a loss of any material benefit to which MGI is entitled.

7.2.5 There is no action, suit, investigation or proceeding pending against, or to the knowledge of MGI, threatened against or affecting, MGI before any court, arbitrator or any governmental authority, including but not limited to regulatory authorities, that in any manner challenges or seeks to prevent, enjoin, alter or materially delay the Contemplated Transactions, and, to the knowledge of MGI, there is no reasonably valid basis for any such action, suit investigation or proceeding to be brought.

7.2.3 The persons executing this Agreement on behalf of MGI are duly authorized to do so and by so doing have bound MGI to the terms and conditions of this Agreement.

ARTICLE 8 - INDEMNITIES AND INSURANCE

8.1 MGI shall be fully liable for and shall defend, indemnify and hold HBP and its Affiliates, officers, directors and employees wholly free and harmless from and against any and all liabilities, damages, losses, costs, taxes, expenses (including reasonable attorneys' fees and other expenses of litigation and

arbitration), claims, demands, suits, penalties, judgements or administrative and judicial orders arising out of or resulting from any claim, suit or proceeding to the extent arising out of or resulting from (a) any failure by MGI, its local distributors or Affiliates to comply with any applicable laws, regulations and/or administrative decision regarding the Products: (b) the storage, distribution, sampling, record-keeping, analysis transfer or sale of the products (c) the promotion, advertising and marketing of the Products; (d) the failure of any Products supplied hereunder to comply with the applicable approved specifications that (i) could have been detected by MGI carrying out visual inspection on the supplied Products with ordinary diligence or (ii) results from

any Products which have been altered, changed, packed or re-packed, processed or otherwise treated other than in strict accordance with HBP's instructions and specifications; or (e) any negligent or wrongful act or omission and/or any breach by MGI or by any of its local distributors and/or Affiliates of any of MGI's obligations, representations and/or warranties hereunder.

8.2 HBP shall be liable for and shall defend, Indemnify and hold MGI and its Affiliates, officers, directors and employees free and harmless from and against any and all liabilities, damages, losses, costs, expenses (including reasonable attorneys' fees and other expenses of litigation and arbitration), claims, demands, suits, penalties, judgments or administrative and judicial orders, arising out of or in any way resulting from any claim, suit or proceeding to the

extent arising out of or resulting from (a) failure of any Products supplied hereunder to conform to the applicable approved specifications, excluding however any liabilities, losses, damages, costs, expenses claims, demands, suits, penalties, judgments or orders resulting from any such non-compliance that (i) could have been detected by MGI carrying out visual inspections on the supplied Products with ordinary diligence or (ii) results from any Products which have been altered, changed, packed or re-packed, processed or otherwise treated other than in strict accordance with HBP's instructions and specifications' or (b) any negligent or wrongful act or omission and/or breach by HBP of any of its obligations and/or warranties hereunder,

8.3 Being understood that each of the parties hereto shall take all reasonable steps to avoid or mitigate any loss, damage or liability which might give rise to a claim under this Agreement, a Party seeking indemnification pursuant to this Article 8 (an "Indemnified Party") shall give prompt and full written notice to the Party from whom such indemnification is sought (the "Indemnifying Party") of the assertion of any claim, or the commencement of any action, suit or proceeding in respect of which indemnity is or may be sought hereunder, provided however that no failure to give such notice or co-operation shall relieve the Indemnifying Party of any liability and/or obligation hereunder (except to the extent the Indemnifying Party has suffered actual prejudice thereby). Subject to any right of Syntex (U.S.A.) LLC under the Syntex Agreement, the Indemnifying Party shall have the sole right to control the defense and settlement thereof, the Indemnified Party will give the Indemnifying Party such information with respect thereto as the Indemnifying Party may reasonably request and will co-operate with the Indemnifying Party in the

defense of said claim, suit or proceeding as the Indemnifying Party may

reasonably request. The Indemnified Party shall not, except at its own cost, voluntarily make any payment or incur any expense with respect to any claim suit or proceeding without the prior written consent of the Indemnifying Party. In addition, the Indemnifying Party shall be subrogated to the rights of the Indemnified Party against any third party, and such Indemnified Party hereby assigns to the Indemnifying Party all claims, causes of action and other rights which the Indemnified Party may then have against any third party, including Affiliates and in the case of HBP, against any contract manufacturer of the Products, with respect to the claim, suit or proceeding which is the subject of the claim for indemnification hereunder. Conversely, and without in any way limiting the obligation of either Party to indemnify the other Party as herein provided, to the extent that either Party shall fail to perform its indemnification obligations under this Article 8, such Party owing a duty of indemnification hereby assigns to the other Party all claims, cause of action and other rights which the Party owing such duty may when have against any third party, including Affiliates and, in the case of HBP, against any contract manufacturer of the Products, with respect to the claim, suit or proceeding.

8.4 MGI shall be solely responsible towards its customers for handling all matters concerning the Products, subject to cooperation with HBP on any recall or other matters that may be injurious to HBP. MGI shall be responsible for any expired Products,

whether stored by MGI and/or its local distributors or returned by wholesalers, pharmacists, doctors, hospitals to whom said products have been sold. HBP shall (i) reimburse to MGI documented reasonable costs incurred by MGI with regard to the destruction of expired Products, up to a maximum quantity of *** of the units of Products sold by MGI in any calendar year and (ii) replace free of charge said expired Products, up to a maximum quantity of *** of the units of Products sold by MGI in any calendar year. Except as provided hereabove, MGI shall not be entitled to any replacement of Products nor to any compensation of any kind from HBP in connection herewith. MGI shall indemnify, defend and hold HBP and its Affiliates, directors, officers and employees wholly free and harmless from and against any and all liabilities, damages, losses, costs, expenses (including reasonable attorneys' fees and other expenses of litigation and arbitration), claims, demands, suits, penalties, judgments or administrative and judicial orders arising therefrom: except with respect to any recall or other regulatory action arising from any breach by HBP or its Affiliates of any warranty, representation or other material obligation contained in this Agreement or the negligence or willful misconduct, of HBP or its Affiliates.

*** Denotes confidential information that has been omitted from the exhibit and filed separately, accompanied by a confidential treatment request, with the Securities and Exchange Commission pursuant to Rule 24b-2 of the Securities Exchange act of 1934.

8.5 Each party shall indemnify and hold the other Party wholly harmless from and against any and all liabilities, damages, losses, costs, expenses (including reasonable attorneys' fees and other expenses of litigation and arbitration), claims, demands, suits, penalties, judgments or administrative and judicial orders arising out of any behavior contrary or in excess to the provisions of Article 13.1 hereunder.

8.6 THE SOLE REPRESENTATIONS AND WARRANTIES THAT HBP MAKES WITH RESPECT TO THE MATTER CONTEMPLATED BY THIS AGREEMENT ARE EXPRESSLY SET FORTH IN ARTICLE 7.1. WITHOUT LIMITING THE GENERALITY OF THE FOREGOING, HBP MAKES NO REPRESENTATION OR WARRANTY OF ANY KIND, EXPRESS OR IMPLIED, OF MARKETABILITY, CAPACITY OR FITNESS FOR A PARTICULAR PURPOSE WITH RESPECT TO THE PRODUCTS. NO ORAL OR WRITTEN REPRESENTATION BY OR ON BEHALF OF HBP SHALL BE INTERPRETED TO CONTAIN ANY SUCH WARRANTY. NEITHER MGI NOR ANY OF ITS EMPLOYEES OR REPRESENTATIVES IS AUTHORISED TO GIVE ANY WARRANTIES OR MAKE ANY REPRESENTATION ON BEHALF OF HBP.

8.7 THE SOLE REPRESENTATIONS AND WARRANTIES THAT MGI MAKES WITH RESPECT TO THE MATTER CONTEMPLATED BY THIS AGREEMENT ARE EXPRESSLY SET FORTH IN ARTICLE 7.2. AND MGI HEREBY DISCLAIMS ALL OTHER REPRESENTATIONS OR WARRANTIES OF ANY KIND, EXPRESS OR IMPLIED. NO ORAL OR WRITTEN REPRESENTATION BY OR ON BEHALF OF MGI SHALL BE INTERPRETED TO CONTAIN ANY SUCH WARRANTY. NEITHER HBP

NOR ANY OF ITS EMPLOYEES OR REPRESENTATIVES IS AUTHORISED TO GIVE ANY WARRANTIES OR MAKE ANY REPRESENTATION ON BEHALF OF MGI.

8.8 NOTWITHSTANDING ANY OTHER PROVISION OF THIS AGREEMENT, NEITHER OF THE PARTIES SHALL BE LIABLE TOWARDS THE OTHER FOR INDIRECT, SPECIAL, PUNITIVE, EXEMPLARY, INCIDENTAL OR CONSEQUENTIAL DAMAGES, INCLUDING WITHOUT LIMITATION LOSS OF PROFITS OR REVENUES, REGARDLESS OF WHETHER SUCH DAMAGES HERE FORESEEABLE OR NOT. THIS CLAUSE WILL HOWEVER NOT BE APPLICABLE IN CASE OF BREACH BY MGI OF THE PURCHASE OBLIGATIONS STATED AT ARTICLE 2 AND BREACH BY EITHER

PARTY OF THE CONFIDENTIALITY AND NON-USE OBLIGATIONS STATED AT ARTICLE 9 OF THIS AGREEMENT.

8.4 Each Party agrees to procure and maintain in full force and effect during the term of this Agreement valid and collectible insurance policies in connection with its activities as contemplated herein. In particular, MGI at its own cost shall cause HBP to be added as additional named insured throughout the term of this Agreement on all policies of general commercial liability insurance and product liability insurance covering MGI, which coverage shall, when MGI either initiates clinical trials on the Products or begins marketing or distributing the Products for commercial sale or for promotional purposes, have limits of

liability which are commercially reasonable in the Territory but shall be not less than USD *** per loss occurrence, within 5 (five) days of the Effective Date and of each beginning of each policy period, MGI shall provide HBP With a certificate evidencing the coverage required hereby and the amount thereof. Such coverage shall be with a reputable insurance company having at least an A.M, Best "A" rating and shall have to be maintained for not less than 6 (six) years following expiration or termination of this Agreement for any reason or if such coverage is of the "claims made" type, for ten years following expiration for termination of this agreement for any reason.

ARTICLE 9 - CONFIDENTIALITY

9.1 MGI shall treat as strictly confidential, and shall use solely for the purpose of and in accordance with this Agreement. any and all information, data and/or document received hereunder or in connection with the Contemplated Transaction not generally known to the trade (all hereinafter referred to as the "Confidential Information"). MGI shall not make such Confidential Information available to any third Party, including any of its Affiliates, except to competent government agencies to which it will be necessary to disclose such information, and in this case (a) strictly to the extent requested by said agencies and (b) only upon exercise of its best efforts to cause said agencies to maintain confidentiality thereof.

9.2 Such Confidential Information shall only be made available to such employees of MGI who are directly and necessarily involved in the authorized use of Confidential Information and who are subject to a secrecy obligation by ***

*** Denotes confidential information that has been omitted from the exhibit and filed separately, accompanied by a confidential treatment request, with the Securities and Exchange Commission pursuant to Rule 24b-2 of the Securities Exchange Act of 1934.

contract, to the extent strictly necessary to perform their duties and obligations hereunder,

9.4 Notwithstanding expiration or termination of this Agreement for any reason, these confidentiality and non-use obligations shall continue until the Confidential Information has become generally known to the public, provided however that nothing contained herein shall in any way restrict or impair the right of MGI to use, disclose or otherwise deal with Information which MGI can demonstrate to HBP by clearly convincing documentation:

9.3.1 is or hereafter becomes part of the public domain through no act or omission of MGI, its employees, Affiliates and/or local distributors, or

9.3.2 MGI was in lawful possession of prior to receipt of the confidential information from HBP, or

9.3.3 previously was, or at any time hereafter is, received in good faith by MGI from sources other than HBP, and/or HHC and which did not originate, directly or indirectly, from Syntex, or

9.3.4 at the time of disclosure, was known by MGI or an Affiliate or local distributor, or after disclosure was independently developed by MGI, an affiliate or local distributor without use of the Confidential Information.

9.4 HBP shall keep strictly confidential, in the same any mutatis mutandis as provided here above for MGI in respect of confidential Information, any MGI confidential information (as defined herein) received from MGI hereunder, except as otherwise specifically provided in this Agreement. As used herein, the term "Confidential Information" shall mean all information disclosed by MGI to HBP, relating to the markets, customers, suppliers, patents or patent applications, inventions, know-how, data or information, products, research and development, procedures, designs, formulas, business plans, financial projections, employees, consultants or any other similar aspects MGI's present or future business, whether such information is disclosed in written, oral, electronic, graphic or other formal.

ARTICLE 10 - FORCE MAJEURE

10.1 Except as set Forth in Section 4.5, if the performance of this Agreement is prevented or restricted by government action, war, fire, explosion, flood, strike, lockout, embargo, act of God, or any other similar cause beyond the control of the defaulting Party, the Party so affected shall be released for the duration of the force majeure, or such other period agreed between the Parties as being reasonable in all circumstances, from its contractual obligations directly affected by the force majeure, provided that the Party concerned shall:

10.1.1 give prompt notice in writing to the ocher Party of the cause of Force majeure:

10.1.2 use all best endeavors to avoid or remove such cause of non-performance;

10.1.3 continue the full performance of this Agreement as soon as such Cause is removed.

10.2 The Parties shall take all reasonable steps to minimize the effects of force majeure on the performance of this Agreement and shall, if necessary, agree on appropriate measures to be taken. Should the force majeure continue for more than 6 (six) months, then the other Party shall have the right to terminate this Agreement forthwith.

10.5 Notwithstanding anything contained in this Article 10, obligations to pay money accruing prior to the force majeure event are never excused by Force majeure.

ARTICLE 11 - TERM

11.1 This Agreement comes into force at the Effective Date hereof, unless terminated earlier pursuant to the provisions hereof, it shall terminate automatically at termination or expiration for any reason of the License Agreement.

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ARTICLE 12 - TERMINATION

12.1 Each of the Parties reserves the right to terminate this Agreement in case of any substantial or persistent breach of any of the terms and conditions of this Agreement by the other Party. The defaulting Party shall be given in writing a 60 (sixty)-day period, except as otherwise specifically provided, to fulfill its obligations hereunder and, if after such period it is still in breach of the Agreement, the other Party shall

have the right to terminate this Agreement by written notice to the defaulting Party. In the event of a breach by MGI of any of the terms and conditions of this Agreement entitling HBP to terminate this Agreement under this Article 12.1, HBP shall immediately and fully inform HHC in writing for appropriate actions by HHC. In particular, MGI hereby acknowledges and agrees that termination of this Agreement by HBP pursuant to this Article 12.1 shall entitle HHC to terminate the License Agreement.

12.2 Either Party snail have the riot to terminate this Agreement upon written notice to the other Party, if such other Party shall become insolvent or shall make an assignment for the benefit of creditors or become involved in receivership, bankruptcy or other insolvency or debtor relief proceedings, or any similar proceedings, or in proceedings, voluntary or forced, whereby the Party involved is limited in the free and unrestrained exercise of its nor judgment as to the carrying out of the terms of this Agreement.

12.3 HBP shall have the right to terminate this Agreement by written notice to MGI if MGI infringes the confidentiality and/or non-use obligations provided for in Article 9 hereabove. MGI shall have the right to terminate this agreement by written notice to HBP if HBP breathes the confidentiality and/or non-use obligations provided for in Article 9.4 hereabove.

12.4 Without limiting the generality of the foregoing, termination or expiration of this Agreement for any reason shall not extinguish any existing claims either of the Parties may have for indemnification and shall not preclude either of the Parties from pursuing any claim for indemnification such Party otherwise may have to the extent that the circumstances giving

rise to such claim arose prior to, on or after the date of termination or expiration.

12.5 Upon expiration or termination of this Agreement for any reason, MGI shall promptly terminate using any and all information and data received hereunder

and return or deliver all such materials to HBP without retaining copies, notes, summaries or translations thereof.

12.6 Unless otherwise set forth herein, the Parties' remedies under this Agreement are intended to be cumulative and net motually exclusive.

ARTICLE 13 - MISCELLANEOUS

13.1 Independent contractor status

The status of HBP and MGI under the business arrangement established by this Agreement is that of independent contractors. MGI shall perform as an independent contractor in relation to both HBP and MGI's customers and. accordingly, MGI shall purchase the Products from HBP or HBP'S nominee and resell then to its customers in its own name and for its own account. MGI has no authority whatsoever to act as an agent or representative of HBP nor any authority or power to contract in the name of or create any liability against or otherwise bind HBP in any way for any purpose, nor shall HBP have such authority or power to so bird MGI.

13.2 Notices

All reports, notices and communications given or made pursuant to this Agreement by one Party to the

other shall be validly given or made for all purposes, in the absence of acknowledgement of receipt, on the date of mailing if mailed by registered airmail or by international courier to the addressee Party at the following addresses, respectively:

HELSINN BIREX PHARMACEUTICALS LTD.
Damastown
Mulhuddart
Dublin 15
Republic of Ireland
For the attention of: General manager

With copy to:

HELSINN HEALTHCARE SA
P.O. BOX 357
6915 Pambio-Noranco
SWITZERLAND
For the attention of regal Department

MGI PHARMA INC.
6300 West Old Shakopee Road
Suite 110
Bloomington
MN 55438-2318, USA
For the attention of: Manager, Legal Affairs

With copy to:

Dorsey & Whitney LLP
220 South Sixth Street
Minneapolis, MN 55402
For the attention of: Timothy S. Hearn

13.3 Binding Effect

Subject to the provisions of article 13.6 herein, this Agreement shall inure to the benefit of, and be binding upon, the respective successors of the Parties.

13.4 Waiver

The failure of a Party to insist upon strict performance of any of the terms and conditions of this Agreement by the other Party shall not constitute a waiver of any of the provisions hereof and no waiver by a Party of any of said terms and conditions shall be deemed to have been made unless expressed in writing and signed by such waiving Party.

13.5 Interpretation

13.5.1 The language of this Agreement is English. No translation into any other language shall be taken into account in the interpretation of the agreement itself.

13.5.2 The headings in this Agreement are inserted for convenience only and shall not affect its construction.

13.5.3 Where appropriate, the terms defined in Article 1 hereabove and denoting a singular number only shall include the plural and vice versa.

13.5.4 References to any law, regulation, statute or statutory provision includes a reference to the law, regulation, statute or statutory provision as from time to time amended, extended or re-enacted.

13.6 Assignment

This Agreement cannot be transferred, sublicensed, assigned or otherwise disposed of (by operation of law or otherwise) by MGI without the prior, written authorization of HBP, which authorization shall not be unreasonably withheld, provided however that MGI shall be entitled to assign this Agreement in conjunction with the assignment of the License Agreement in accordance with the terms and conditions thereof, HBP shall have the right to assign or transfer, in whole or in part, this Agreement to any of its Affiliates.

13.7 Statements to the Public

Neither HBP nor MGI shall make or procure or permit the molting of any announcement or statement to the public with respect to this Agreement its subject matter or any ancillary ratter without the prior consent of the other Party, which consent shall not be unreasonably withheld. The wording and the timing of any press release or of any other announcement and/or statement to the public shall have to be agreed upon in advance between the Parties.

Nothing herein shall prohibit MGI from disclosing information to the extent required by the U.S. Securities and Exchange Commission, Nasdaq or other similar authorities. It is however understood and agreed that (a) the contents of any copy of this Agreement, or of any other agreement between the Parties, which has to be sent to the SEC shall have to be previously agreed upon between the Parties and shall be in redacted form to maintain the confidentiality of proprietary and/or competitivity sensitive information, and (b) MGI shall use its best efforts to obtain authorization by the SEC to keep confidential any information which is deemed to be

confidential by the Parties or any of than or which may, in either Parry's opinion, put a competitive advantage to third parties.

13.8 Expenses

Unless specifically and expressly provided for to the contrary in this Agreement, each of the Parties shall bear its own expenses incurred in connection with the performance of this Agreement.

13.9 Survival

The following provisions shall survive expiration or Termination of this Agreement for any reason: Articles 1 (whole clause), 6 (whole clause), 8 (whole clause), 9 (whole clause), 12.4 through 12.6, 13 (whole clause), 15 (whole clause) and 16 (whole clause),

ARTICLE 14 - APPENDICES

14.1 The following Appendices shall be an integral part of this Agreement:

Appendix 1: Products

Appendix 2: Price

ARTICLE 15 - LAW TO GOVERN An ARBITRATION

15.1 This Agreement shall he governed by and construed in accordance with the law of Switzerland.

15.2 It is the express decision of the Parties that any dispute which may arise between the Parties concerning this Agreement, which cannot be settled amicably, shall be submitted to arbitration for final decision. Also, any dispute as to the applicability of the arbitration clause shall be subject to arbitration.

Notwithstanding the above, each Party expressly reserves the right to seek judicial relief from a court of competent jurisdiction if the other Party is or appears to be in violation of such other Party's obligations of non-use and non-disclosure under Article 9 above, including, without limitation, any injunction or other preliminary relief.

15.3 It is expressly agreed that arbitration shall be held in English language in Geneva (Switzerland) and conducted under the Rules of Arbitration of the International Chamber of Commerce. The court of arbitration shall consist of three arbitrators. Each Party is entitled to nominate one arbitrator. If, within one month after receipt of the request for arbitration filed by one Party, the other has not yet appointed an arbitrator, such arbitrator shall be appointed by the International Court of Arbitration of the International Chamber of Commerce on request of the first Party. The two arbitrators shall nominate the president of the court of arbitration, who shall be a lawyer qualified to practice and currently practicing as an attorney-at-law or as a judge. If they cannot come to terms within one month, the president of the court of arbitration shall be nominated by the International Court of Arbitration of the International Chamber of Commerce, on request of the more diligent Party.

15.4 If one of the arbitrators in unable to fulfil his/her duties for any reason the Party having nominated him/her shall nominate another arbitrator within one month,

otherwise this arbitrator will be nominated by the international Court of Arbitration of the International Chamber of Commerce.

15.5 If the arbitrators or the president have to be replaced, the proceedings do not have to be started anew and will continue at the point where they were stopped.

15.6 The court of arbitration is hereby expressly instructed to act with most diligence and to keep any term as short as possible and to render the decision as soon as possible.

15.7 The Parties hereby stipulate that any arbitration hereunder shall be subject to the following rules: (a) the arbitrators may not award or assess punitive damages against either Party; and (b) each Party shall bear its own costs and expanses of the arbitration and one-half (1/2) of the fees and costs of the arbitrators, subject to the power of the arbitrators, in their sole discretion, to award all such reasonable costs, expenses and fees to the prevailing Party.

15.8 The Parties agree that the arbitrator's award shall be the sole and exclusive remedy between them regarding any claims, counter-claims, issues or accountings presented or pled to the arbitrator and that any costs, fees or taxes incident to enforcing the award shall be, to the maximum extent permitted by law, charged against the Party resisting such enforcement.

15.9 Notwithstanding the foregoing, any Party may bring a case of action against the other Party before any court of competent jurisdiction at the domicile of the defendant Party, if and to extent that any arbitral award rendered in the arbitration proceedings is unenforceable.

15.10 Subject to the provisions of article 15.9 in the event that an award is rendered pursuant to this Article 15 by an arbitrator in favor of HBP, the Parties acknowledge and agree that such award shall be enforceable by HBP, and MGI hereby consents so the exclusive jurisdiction for purposes of enforcement of any such award against MGI to the United States District Court for the District of Delaware, or, if jurisdiction or venue cannot be laid therein, the jurisdiction of any courts in the State of Delaware. Each of the Parties hereby consents to the exclusive jurisdiction of such courts (and of the appropriate appellate courts) for the purposes set forth above.

ARTICLE 16 - ENTIRETY OF AGREEMENT AND SEVERABILITY

16.1 This Agreement supersedes all prior agreements and understandings, whether oral or written, made by either Party or between the Parties and constitutes the entire Agreement of the Parties with regard to the subject matter hereof. The Parties however acknowledge and understand that (a) the existence and validity of this Agreement depend upon and are conditional upon the existence and validity of the License Agreement and (b) in case of any discrepancy between the License Agreement and this Agreement, this agreement shall be construed in a manner consistent with the License Agreement. This Agreement shall not be considered extended, cancelled or amended in any respect unless done so in writing and signed on behalf of the Parties hereto.

16.2 The Parties hereby expressly state that it is the intention of neither Party to violate any rule, law

and regulations. If any provision of this Agreement is rendered invalid or unenforceable, the Parties agree to renegotiate such provision it good faith and to replace it with valid and enforceable provisions in such a way as to reflect as nearly as possible the intent and purpose of the original provision.

IN WITNESS WHEREOF, the Parties hereto have caused this Agreement to be executed in duplicate by their duly authorized officers.

For and on behalf of
HELSINN BIREX PHARMACEUTICALS Ltd

/s/ Riccardo Braglia
Riccardo Braglia
Proxy

/s/ Enrico Braglia
Enrico Braglia
Proxy

For and on behalf of
MGI PHARMA, INC.

/s/ Charles N. Blitzer
Charles N. Blitzer
President and Chief Executive officer

/s/ Leon O. Moulder, Jr.
Leon O. Moulder, Jr.
Executive Vice President

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Exhibit 99.3

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NEWS RELEASE

FOR IMMEDIATE RELEASE
March 22, 2001

CONTACT:
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MGI PHARMA INITIATES NEW PHASE 2 TRIAL OF IROFULVEN FOR OVARIAN CANCER

New Phase 2 Trial to Evaluate Every-Other-Week Dosing schedule

MINNEAPOLIS, March 22, 2001 – MGI PHARMA, INC., (Nasdaq: MOGN) today announced that it has initiated a new Phase 2 clinical trial of irofulven, its novel anticancer compound, for patients with refractory or recurrent advanced epithelial ovarian cancer. This multi-center phase 2 trial will evaluate irofulven using an every-other-week dosing schedule in up to 65 patients to develop recommendations for an anticipated Phase 3 trial with irofulven in advanced ovarian cancer. This trial is being conducted based in part upon the anti-cancer activity seen in trials sponsored by MGI and sponsored by the National Cancer Institute (NCI). Tumor shrinkage, including a complete response in the NCI Phase 2 ovarian cancer trial, and a complete response in an

ovarian cancer patient using the every other week dosing schedule in a dose optimization trial, have prompted further development of irofulven for the treatment of ovarian cancer. The intermittent, every-other-week dosing schedule for irofulven is being used based upon the greatly improved tolerance and demonstrated anti-cancer activity that was seen with this schedule in the dose optimization trial. The patient enrollment period for this Phase 2 trial is expected to last approximately 12-18 months.

"We are excited to further explore the activity that has been demonstrated in earlier trials of irofulven for ovarian cancer patients," said Dr. David S. Alberts, professor of medicine, pharmacology and public health and associate dean for research, College of Medicine and Arizona Cancer Center, University of Arizona and lead investigator for MGI's trial. "Because of the evidence and anti-tumor activity seen in ovarian cancer patients who have failed prior therapies, and because of the improved tolerance and diminished toxicity with the new dosing schedule, we are eager to determine irofulven's role in treating these patients."

Ovarian cancer is the leading cause of gynecological cancer deaths among women in the United States. The American Cancer society estimated that approximately 23,100 new cases of ovarian cancer were diagnosed and 14,000 women died from the disease in the U.S. in 2000. Worldwide, 166,000 new cases of ovarian cancer and 101,000 deaths are estimated to occur

annually. The current first-line treatment of advanced ovarian cancer consists mainly of surgery followed by combination chemotherapy consisting of paclitaxel (Taxol(R)) and carboplatin (Paraplatin(R)), the two most commonly prescribed drugs.

"Most ovarian cancer patients will eventually develop platinum- and paclitaxel-resistance, and salvage chemotherapy in this group is each into effective than first-line therapy," notes Dr. John MacDonald, MGI's senior vice president of research and development. "That's why chemotherapeutics with novel mechanisms of action, such as irofulven, are attractive agents to test against the drug-resistant tumors. The need for new agents in this area is huge, and we are focused on addressing these unmet needs of cancer patents."

Results of Irofulven in Ongoing Ovarian Cancer Trials

MGI PHARMA is studying irofulven in refractory ovarian cancer patients who have had tumor growth during their first-line treatment or within six months following that treatment. Interim results from MGI's ongoing Phase 2 trial of irofulven in ovarian cancer indicate that of the 78 patients evaluable for objective response:

- one patient achieved the primary endpoint of a confirmed partial response;
- one patient experienced a partial response that was observed in only the first of two

measurements required for a confirmed partial response; and

- one patient experienced stable disease and received four cycles of treatment.

The NCI is conducting a Phase 2 trial of irofulven for the treatment of ovarian cancer in patients with recurrent or persistent disease. Irofulven was administered daily for 4-5 days every 28 days, in a presentation at the annual meeting of the American Association of Cancer Research (AACR) in April 2000, the principal investigator for the MGI trial concluded that irofulven is an active agent an ovarian cancer patients with recurrent or persistent disease and that further studies are warranted. Interim results from the first 27 patients enrolled in the trial include the following:

- one patient achieved complete clinical response, the disappearance of measurable disease;
- five patients achieved the primary endpoint of a partial response, with two responses lasting more than one year; and
- Seven patients experienced stable disease, ranging up to nine months.

About Irofulven

Irofulven (also known as MGI 114, hydroxymethylacylfulvene, or HMAF) is the first product candidate being developed by MGI PHARMA from its family of proprietary anti-cancer compounds called acylfulvenes. Irofulven is currently being tested in a series of clinical trials for

the treatment of solid tumors, across a variety of cancers. Irofulven has demonstrated promising anti-tumor activity as a single agent in clinical testing against pancreatic, ovarian and prostate cancers. In February 2001, MGI PHARMA initiated a pivotal Phase 3 trial of irofulven in advanced-stage, refractory pancreatic cancer patients. side effects from irofulven are comparable to those seen with marketed chemotherapies and include bone marrow suppression (decreases in platelets or white blood cell counts), nausea, vomiting and fatigue. Patients and healthcare providers seeking information on the various irofulven clinical trials may call MGI PHARMA's medical communications Help Line at 1-850-562-5580 or the National Cancer Institute's Cancer Information Service at 1-800-4-CANCER (TTY 1-800-332-8615).

About MGI PHARMA

MGI PHARMA, INC. is an oncology-focused pharmaceutical company that acquires, develops and commercializes proprietary products that meet patient needs. MGI PHARMA focuses its sales efforts solely in the United States and collaborates with other pharmaceutical or biotechnology companies for its products in international markets. For more information about MGI PHARMA, please visit the company's web site at www.mgipharma.com.

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not guarantees of future performance and involve a number of risks and uncertainties that may cause the company's actual results to differ materially from the results discussed in these statements. Factors that might affect MGI PHARMA's results include, but are not limited to the ability of MGI PHARMA's product candidates, such as irofulven, to be proven safe and effective in humans and to ultimately compete successfully with other therapies, continued sales of MGI PHARMA's marketed products, development or acquisition of additional products, reliance on contract manufacturing, changes in strategic alliances, and other risks and uncertainties detailed from time to time in the Company's filings with the Securities and Exchange Commission. MGI PHARMA does not intend to update any of the forward-looking statements after the date of this news release to conform them to actual results.

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NEWS RELEASE

FOR IMMEDIATE RELEASE
March 28, 2001

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MGI PHARMA PRESENTS FURTHER DATA ON IROFULVEN'S ANTI-TUMOR ACTIVITY AT AACR MEETING

MINNEAPOLIS, March 28, 2001 – MGI PHARMA, INC., [Nasdaq: MOGN) today announced that six poster presentations on irofolven's anti-tumor activity and mechanism of action were made at this year's American Association for Cancer Research (AACR) meeting held in New Orleans from March 24 - 28, 2001. The preclinical data presented serves as the basis for MGI's plans to expand the clinical development of irofulven in a variety of cancers.

In one presentation, complete regressions of hormone-refractory human DU-145 prostate tumors growing in nude mice were reported when irofulven was used in combination with Taxotere(R) (docetaxel). complete regressions were observed in 17 of 20 animals administered the drugs in combination, whereas Taxotere alone produced no complete regressions and a submaximal dose of irofulven produced complete regressions in two of 10 animals. MGI now plans to initiate a Phase 1 clinical trial to evaluate this promising drug combination in cancer patients.

Another investigation reported on the activity of irofulven in combination with other anti-cancer agents in human tumor cell lines and drug-resistant human tumor xenografts. Irofulven combined with taxanes, topoisomerase I inhibitors, mitomycin C, thiotepa, or carboplatin exhibited statistically significant synergistic (or greater than additive) anti-tumor effects. Such activity suggests a basis for possible new clinical investigations.

Complete regressions were also reported following irofulven treatment of mice bearing glioblastoma xenografts. Glioblastoma is a particularly lethal form of brain tumor for which the limited treatment options provide minimal benefit. This investigation demonstrated the ability of irofulven to cross the blood-brain barrier in an active form. MGI also intends to initiate a Phase 2 trial to evaluate irofulven's activity in this particularly challenging tumor target.

Three additional presentations on irofulven's preclinical activity further characterize the mechanism by which irofulven induces apoptosis in human breast, prostate, and pancreatic tumor cell lines.

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About Irofulven

Irofulven (also known as MGI 114, hydroxymethylacylfulvene, or HMAF) is the first product candidate being developed by MGI PHARMA from its family of proprietary anticancer compounds called acylfulvenes. Irofulven is currently being tested in a series or clinical trials for the treatment of solid

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About MGI PHARMA

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EDITORS' NOTE: Abstracts presented on irofulven at AACR include:

#475 Antitumor Activity of Irofulven (MGI 114) in Combination with Taxotere against DU145 Human Prostate Tumor Xenograft model.

#476 Activity of Irofulven (MGI 114, HMAF) in Combination with other Chemotherapeutic Agents.

#1753 Activity of Irofulven (6-Hydroxymethylacylfulvene, MGI 114) in the Treatment of Human Central Nervous System Tumors Growing in Athymic Nude Mice.

#3443 Caspase 3 Is Not Required for Apoptosis by Irofulven (Hydroxymethylacylfulvene).

#3444 Irofulven-Induced Apoptosis in Human Pancreatic Cancer Cells is Mediated by Activation or ERK and JNK Kinases.

#3445 Early Events in Apoptosis Induced by Irofulven (Hydroxymethylacylfulvene) in Prostate Tumor Cells.

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Exchange Commission. MGI PHARMA does nor intend to update any of the forward-looking statements after the date of this news release to conform them to actual results.

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NEWS RELEASE

FOR IMMEDIATE RELEASE
April 10, 2001

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MGI PHARMA SIGNS EXCLUSIVE LICENSE AGREEMENT WITH HELSINN HEALTHCARE SA, FOR PALONOSETRON, A PHASE 3 ANTI-EMETIC

MINNEAPOLIS and LUGANO, SWITZERLAND, April 10, 2001 - MGI PHARMA, INC., (Nasdaq: MOGN) and Helsinn Healthcare SA, a privately owned pharmaceutical group with headquarters in Switzerland, today announced that they have signed the definitive agreement granting MGI PHARMA exclusive North American license and distribution rights to palonosetron. The signing of the letter of intent for this agreement was previously announced in February. Palonosetron is a potent and selective 5-HT3 antagonist with an extended half-life, in Phase 3 development for the prevention of chemotherapy-induced nausea and vomiting (CINV). Completion of the Phase 3 trials could allow for NDA. (New Drug Application) submission in the first half of 2002. When launched, palonosetron will compete in the $1 billion North American CINV market.

"We are looking forward to entering the supportive care segment of oncology, the successful completion of the Phase 3 program and approval process for palonosetron, and the opportunity to demonstrate the role that this novel agent can have in preventing chemotherapy-induced nausea and vomiting for cancer patients," commented Chuck Blitzer, president and CEO of MGI PHARMA. "Palonosetron is another exciting addition to our growing oncology product portfolio, representing another well-advanced product that can be commercialized in the near term."

"Palonosetron is our first product entry into the United States, and we are pleased to be working with MGI PHARMA for the North American distribution of this innovative product in the supportive care segment

of oncology," commented Riccardo Braglia, managing director of HELSINN. "We know that MGI PHARMA's proven commercial organization, its experienced oncology sales force, and its present and future commitment to palonosetron's role within the 5-HT3 antagonist marketplace will ensure the success of our new partnership."

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About Palonosetron

When launched as a marketed product, palonosetron will be one of four products competing in the $1 billion north American market for 5-HT3 antagonists. The extended half-life of palonosetron as compared to the other agents and the results of Phase 2 trials assessing efficacy beyond 24 hours differentiates Palonosetron from the three currently marketed 5-HT3 antagonists indicated for CINV.

CINV in estimated to occur in 85 percent of cancer patients undergoing chemotherapy and can result in delay or even discontinuation of treatment, and the advent of 5-HT3 antagonists has revolutionized the management of nausea and vomiting experienced by cancer patients undergoing chemotherapy.

Palonosetron has been tested in a randomized, double-blind dose-ranging Phase 2 Trial at multiple sites throughout the U.S. that evaluated its efficacy and safety when administered in a single intravenous dose for the prevention of nausea and vomiting in patients receiving highly emetogenic chemotherapy. over 1,000 patients have participated in Phase 3 and

Phase 2 trials of palonosetron. Based on these results, Helsinn initiated a Phase 3 clinical trial program that is intended to enroll more than 1,900 patients in several well-controlled, double-blind trials comparing palonosetron to currently available 5-HT3 antagonists - at approximately 80 centers in North America and Europe. Based on the extended half-life of palonosetron and the results of the Phase 2 trial, its efficacy will be assessed over Day 2 through Day 5 following treatment, in addition to the primary efficacy measure of complete response during the 24-hour period after the start of chemotherapy. The most frequent adverse events associated with palonosetron are similar to those seen with other 5-HT3 antagonists and include headache and constipation.

Under the terms of the exclusive license agreement, MGI PHARMA will make $11 million in upfront payments, already including the initial $5 million made upon signature of the letter of intent, and will make additional payments based on the achievement of certain milestones through the approval of palonosetron in the U.S. Helsinn will continue to fund and conduct all development of palonosetron. MGI PHARMA will also pay royalties and product supply fees based upon net sales. Helsinn will supply finished product ready for distribution, the active ingredient of which is manufactured at Helsinn's new state-of-the-art facility (Helsinn Advanced Synthesis SA) dedicated to the production of high potency active ingredients.

About MGI PHARMA

MGI PHARMA, INC. is an oncology-focused pharmaceutical company that acquires, develops and commercializes proprietary products that meet patient needs and build shareholder value. MGI

focuses its sales efforts solely in the United States and collaborates with other pharmaceutical or biotechnology companies for its products in international markets. For more information about MGI, please visit the Company's web site at www.mgipharma.com.

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About HELSINN HEALTHCARE SA

Helsinn (www.helsinn.com) is a privately owned pharmaceutical group with headquarters in Switzerland. Helsinn's core business is licensing. The company's business strategy is to in-license new chemical entities at a certain stage of development. Helsinn completes the development by performing pre-clinical and clinical studies as well as chemical and pharmaceutical development through the attainment of market approval in strategic markets (USA and Europe). The finished products and active pharmaceutical ingredients are manufactured at Helsinn and supplied to its marketing partners for distribution.

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safe and effective in humans and to ultimately compete successfully with other therapies, development or acquisition of additional products, continued sales of MGI PHARMA's marketed products, reliance on contract manufacturing, changes in strategic alliances, and other risks and uncertainties detailed from time to time in the company's filings with the Securities and Exchange Commission, MGI PHARMA does not intend to update any of the forward-looking statements after the date of this news release to conform them to actual results.

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NEWS RELEASE

FOR IMMEDIATE RELEASE
April 12. 2001

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MGI PHARMA INITIATES ADDITIONAL PHASE 2 TRIAL OF IROFULVEN IN HORMONE-REFRACTORY PROSTATE CANCER

Phase 2 Trial to Evaluate Every-Other-Week Dosing Schedule

MINNEAPOLIS, April 12, 2001 – MGI PHARMA. INC., (Nasdaq: MOGN) today announced that it has initiated an additional phase 2 clinical trial of irofulven, its novel anti-cancer compound, using an intermittent dosing schedule to treat hormone-refractory, prostate cancer patients. This randomized, multi-center Phase 2 trial conducted in Europe will evaluate the anti-tumor activity, safety, and clinical benefit of irofulven as a single agent and in combination with prednisone. Up to 54 patients will be treated with irofulven on an every-other-week dosing schedule. Results from this Phase I trial will be used to develop recommendations for an anticipated Phase 3 trial with irofulven in prostate cancer. Decrease in PSA (prostate-specific antigen) is the primary endpoint, along with objective tumor response in patients with measurable disease. Time to disease progression, duration of response, overall survival and clinical benefit will also be assessed. The patient enrollment period for this Phase 2 trial is expected to last approximately 18 months.

The anti-tumor activity of irofulven in hormone-refractory prostate Cancer patients has already been evaluated in a prior Phase 2 trial where irofulven was dosed daily for five days every 28 days. All of the 32 patients who were evaluable for PSA response had stable or decreasing PSA levels and four of those patients had partial PSA responses (defined as a decrease of at least 50 percent for at least one month).

In addition, one of the nine patients who had measurable disease had an objective partial response.

Improved tolerance and an ability to deliver more drug over multiple courses of treatment has been observed in an ongoing dose-optimization trial using an every-other-week dosing schedule, which will be assessed in this new trial. This new multi-center Phase 2 trial of irofulven, in patients with hormone-refractory prostate cancer, used alone or in combination with prednisone, will provide us with valuable additional insight about irofulven's role in treating this type of cancer," said Professor Stephane Culine, head of the medical oncology department of Val d'Aurelle-Paul Lamarque Anticancer Center at Montpellier in France. And the lead Investigator for the trial. "Considering the anti-tumor activity shown in a previous Phase 2 trial and a new dosing schedule that is better tolerated, we hope to demonstrate further evidence of irofulven's efficacy in this disease."

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Dr. John MacDonald, senior vice president of research and development at MGI PHARMA commented, "Our continued research in this area demonstrates MGI's commitment to addressing the unmet needs of cancer patients, and hormone-refractory prostate cancer is clearly an area where we hope irofulven will make a difference in patients' lives."

About Hormone-Refractory Prostate Cancer

In men, carcinoma of the prostate is the second highest cause of cancer-related death after lung cancer, with an estimated 198,100 new cases to be diagnosed and 31,500 anticipated deaths in the United States in 2001, according to the American cancer society. Worldwide, the incidence of microscopic prostate malignancy increases from 30 percent in men over 50 years in age, to more than 50 percent in men in their eighties. The standard treatment for local disease is either radical prostatectomy or pelvic irradiation. Approximately 20 to 30 percent of men with prostate cancer have distant metastases at the time of diagnosis.

Hormone therapy is the first therapy to show efficacy in reducing tumor growth, but the duration of the response averages only 12 to 18 months. Among patients with disseminated disease, 70 to 80 percent experience subjective symptomatic relief, and approximately 40 to 50 percent achieve objective remission. Second-line hormonal therapy provides clinical improvement in only 10 to 20 percent of such patients, has a duration of less than six months, and does not significantly improve survival, indicating that a large number of patients become hormone-refractory after first-line treatment. Chemotherapy has been of limited value in the management of patients who have become refractory to hormone therapy. Despite many years of effort to develop effective chemotherapy administered before, during, or after hormone therapy, few effective drugs have been identified.

Advanced clinical trials are needed to compare the current standard treatment of mitoxantrone in combination with prednisone to other drug combinations to

identify the best combination for improving quality of life and positively affecting survival.

About Irofulven

Irofulven (also known as MGI 114, hydroxymethylacylfulvene, or HMAF) is the first product candidate being developed by MGI PHARMA from its family of proprietary anti-cancer compounds called acylfulvenes. Irofulven is currently being tested in a series of clinical trials for the treatment of solid tumors, across a variety of cancers. Irofulven has demonstrated promising anti-tumor activity as a single agent in clinical testing against pancreatic, ovarian and prostate cancers. In February 2001, MGI PHARMA initiated a pivotal Phase 3 trial of irofulven in advanced-stage, gencitabine-refractory pancreatic cancer patients. Side effects from irofulven are comparable to those seen with marketed chemotherapies and include bone marrow suppression (decreases in platelets or white blood cell counts), nausea, vomiting and fatigue. Patients and health care providers seeking information on the various irofulven clinical trials may call MGI PHARMA Medical communications Help Line at 1-800-562-5580 or the National Cancer Institute's cancer Information Service at 1-800-4-CANCER (TTY 1-800-332-8515).

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Exhibit 99.7

[MGI LOGO]

NEWS RELEASE

FOR IMMEDIATE RELEASE
April 18, 2001

CONTACT:
Maggie P. Knack
Director. Investor Relations
952-346-4771
IR@mgipharma.com

MGI PHARMA REPORTS 2001 FIRST QUARTER RESULTS

Company Portfolio Now Includes Three Key Marketed Products & Two Phase 3 Compounds: Reports Record Salagen(R) Tablets Sales

MINNEAPOLIS, April 18, 2001 – MGI PHARMA, INC., (Nasdaq: MOGN) today reported that product sales revenue increased 53 percent to $7.0 million: in the first quarter ended March 31. 2001, from 54.6 million in the first quarter of 2000. Total revenues increased 46 percent to $7.6 million in the 2001 first quarter from $5.2 million in the first quarter a year ago, total costs and expenses increased 98 Percent to $11.1 million in the 2001 first quarter from $5.6 million in the 2000 first quarter. The Company reported a net loss of $3.1 million, or $0.19 per share, in the first quarter of 2001 compared to a net loss of $9.5 million, or $0.63 per diluted share, in the first

quarter of 2000. As previously noted, the prior year's results have been restated for the effect of implementing Staff Accounting Bulletin 101 as of January 1, 2000 and resulted in in charge of $9.4 million, or $0.62 per share, it the first quarter of 2000.

The quarter's strong performance in product sales revenue was primarily due to growth in sales of Salagen(R) Tablets (pilocarpine hydrochloride) and from two recent oncology product additions, Hexalen(R) capsules (altretamine) and Mylocel(TM) Tablets (hydroxyurea). The increase in costs and expenses was primarily due to an increase in research and development expense related to the expanded development of two product candidates, irofulven and MG98, the recent promotional launches of new products, and an increase in selling expenses for the expansion of the sales organization which principally occurred in the second quarter of 2000.

"We continue to deliver on our business plan by expanding our marketed product portfolio and accelerating our clinical development programs for irofulven and MG98," said Chuck Blitzer, president and CEO of MGI PHARMA. "At the same time, our experienced marketing team and oncology sales force is delivering a record quarter performance in product sales. The first quarter of 2001 includes sales from both Hexalen capsules and Mylocel Tablets, for which we began direct promotion in March, in addition to the steadfast sales performance of Salagen Tablets, our flagship commercial product. MGI is making great strides toward our goal of becoming a leader in oncology."

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Recent Company Highlights

Clinical Developments:

- Initiated a pivotal Phase 3 clinical trial of irofulven, its novel anti-cancer compound, for patients with advanced-stage pancreatic cancer. The trial is a randomized, multi-center, international trial in advanced-stage pancreatic cancer patients whose disease progressed after treatment with gemcitabine, the current standard-of-care treatment.
- Initiated a Phase 2 clinical trial of irofulven for patients with refractory or recurrent advanced ovarian cancer.
- Initiated another Phase 2 clinical trial of irofulven to treat hormone-refractory prostate cancer patients. This randomized, multi-center Phase 2 trial conducted in Europe will evaluate the anti-tumor activity, safety, and clinical benefit of irofulven as a single agent and in combination with prednisone.
- Made six poster presentations on irofulven's anti-tumor activity and mechanism of action at this year's American Association for Cancer Research (AACA) meeting held in March. The preclinical data presented serves as the basis for MGI's plans to expand the clinical development of irofulven in a variety of cancers both as a single agent and in combination with other drugs.

In-licensed Products:

- Signed definitive agreement granting MGI PHARMA exclusive North American license and distribution rights to palonosetron, a potent and selective 5-HT3 antagonist with an extended half-life, in Phase 3 development for the prevention of chemotherapy-induced nausea and waiting (CINV) with Helsinn Healthcare SA. When launched, palonosetron would compete in the $1 billion North American CINV market. In addition to the previously disclosed $11 million in upfront payments that became due upon signing the definitive agreements. MGI PHARMA is obligated to pay a total of $27 million in milestone payments upon achievement of the underlying development objectives, including marketing approval of palonosetron in the United States. Helsinn will continue to fond and conduct all development of palonosetron.

- Signed exclusive agreement for the U.S. marketing and distribution rights for Mylocel tablets, a recently FDA-approved oral tablet formulation of hydroxyurea for the treatment of certain malignancies, with Barr Laboratories, Inc.

- Launched exclusive promotion of Hexalen Capsules (altretamine) and Mylocel Tablets (hydroxyurea) in the U.S. oncology market.

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2001 Financial Outlook

This section provides forward-looking information about MGI PHARMA's financial outlook for 2001. These projections include the impact of MGI PHARMA's entire product portfolio, which comprises Salagen(R) Tablets, Hexalen(R) capsules. Mylocel(TM) Tablets, irofulven and the other acylfulvenes, palonosetron, MG98 and the complementary small molecule inhibitor program. The disclosure notice paragraph regarding forward-looking statements at the end of this news release to especially applicable to this section. For the year ending December 31, 2001:

- Product sales are currently projected to grow 15 to 20 percent. (increased from last quarter guidance)
- Cost of product sales as a percent of sales revenue is expected to range from 10 to 15 percent,
- Licensing revenue is expected to approximate the annual 2000 amount after application of SAB 101, and would increase if commercial rights for irofulven outside the United States are out-licensed.
- R&D expense is expected to range from $35 to $45 million depending on the pace of irofulven and MG98 development and the timing of palonosetron milestone achievements.
- Selling, general and administrative expenses are expected to be approximately $25 million or less, (decreased from last quarter guidance)

- Amortization expense related to the acquisition of Hexalen Capsules is expected to be approximately $1.2 million, and
- Net loss is expected to range from $35 to $45 million.

Webcast of First Quarter Conference Call

MGI PHARMA will broadcast ins 2001 first quarter results in an investor conference call live over the Internet on Wednesday, April 18, 2001 at 1:00 p.m. Eastern Time. The company's executive management team will review first quarter 2001 financial results, answer questions from analysts and investors, and provide commentary on MGI's product portfolio and business outlook. All interested parties are welcome to log on to www.mgipharma.com to listen to the webcast, which will also be archived on the company's web site.

About MGI PHARMA

MGI PHARMA, INC. is an oncology-focused pharmaceutical company that acquires, develops and commercializes proprietary products that meet patient needs and build shareholder value. MGI focuses its sales efforts solely in the United States and collaborates with other pharmaceutical or biotechnology companies for its products in international markets. For more information about MGI please visit the company's web site at www.mgipharma.com.

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This news release contains forward-looking statements that may include statements regarding intent, belief or current expectations of the Company and its management. These forward-looking statements are not guarantees of future performance and involve a number of risks and uncertainties that may cause the company's actual results to differ materially from the results discussed in these statements. Factors that might affect MGI PHARMA's results include, but are not limited to the ability of MGI PHARMA's product candidates to be proven safe and effective in humans and to ultimately compete successfully with other therapies, continued sales of MGI PHARMA's commercial products, development or acquisition of additional products, reliance on contract manufacturing, changes in strategic alliances, continued access to capital, and other risks and uncertainties detailed from time to time in the company's filings with the Securities and Exchange Commission. MGI PHARMA does not intend to update any of the forward-looking statements after the date of this news release to conform them to actual results.

(more)

MGI PHARMA, INC.
Statements of Operations
(Unaudited)

	Three Months Ended March 31.	
	2000	2001
Revenues:		
Sales	$4,566,295	$6,984,108
Promotion	250,000	0
Licensing	361,056	591,669
	5,177,351	7,575,777
Costs and Expenses:		
Cost of sales	304,071	789,353
Selling, general and administrative	3,520,584	6,492,775
Research and development	1,804,218	3,553,818
Amortization	0	295,494
	5,628,873	11,131,440
Loss before interest and taxes	(451,522)	(3,55,663)
Interest income	372,846	436,166
Loss before taxes	(78,676)	(3,119,497)
Provision for income taxes	61,279	0
Loss before cumulative effect of change principle	(139,955)	(3,119,497)

Cumulative effect of change is accounting principle	(9,402,643)	0
Net loss	$(9,542,598)	$(3,119,497)
Net loss per common share:		
Basic		
Loss before effect of accounting change	$(0.01)	$(0.19)
Cumulative effect of accounting change	(0.62)	0.00
Net loss	$(0.63)	$(0.19)
Assuming dilution		
Loss before effect of accounting change	$(0.01)	$(0.19)
Cumulative effect of accounting change	(0.62)	0.00
Net loss	$(0.63)	(0.29)
Weighted average number of common shares:		
Basic	15,217,199	16,532,670
Assuming dilution	15,217,199	16,532,670

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Balance Sheet Data
(unaudited)

	December 31, 2000	March 31, 2001
Cash and short term investments	$29,898,787	$23,864,961
Total assets	52,743,570	48,612,974
Total stockholders' equity	26,045,617	23,918,230

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NEWS RELEASE

FOR IMMEDIATE RELEASE
April 25, 2001

CONTACT:
Maggie P. Knack
Director, Investor Relations
952-346-4771
IR@mgipharma.com

MGI PHARMA AMNOUNCES ISSUANCE OF KEY PATENT FOR INHIBITION OF DNA METHYLTRANSFERASE

MINNEAPOLIS, April 25, 2001 MGI PHARMA, INC., (Nasdaq: MOGN) today announced that a key patent for "Inhibition of DNA methyltransferase" was recently granted to MethylGene Inc., its partner with whom the Company has an exclusive North American license, research and development agreement for inhibitors of DNA methyltransferase. As part of its existing agreement with MethylGene, MGl PHARMA has the exclusive license to develop, market and sell in North America MG98, a second-generation mRNA inhibitor, and any small molecule inhibitor of DNA methyltransferase derived from the two companies' research collaborations. This new patent provides significant expansion of the intellectual property rights available under this exclusive agreement.

U.S. Patent No. 6,184,211 is entitled "Inhibition of DNA Methyltransferase" and covers the administration of an agent that could allow the human body to restore normally occurring mechanisms to slow or stop the growth of cancerous tumors. DNA methyltransferase is an enzyme that inhibits the expression of genes that would otherwise slow or stop tumor growth. When DNA methyltransferase is over-expressed end hypermethylation occurs, tumor suppressor genes may be "turned off." Hypermethylation, in conjunction with cancerous conditions, can allow cancer cells to proliferate. Hypermethylation of tumor suppressor genes has been observed to occur in a wide variety of human cancers. Recent findings also suggest that the extent of tumor suppressor gene methylation correlates with disease progression for a variety of tumor types. In addition, it appears this enzyme also affects

the expression of other key genes involved in cancer progression, Such as DNA repair genes and hormone receptors.

"The role of DNA methylation in the causation and progression of human cancer is an area of very active recent research. Our research with MethylGene has demonstrated that selective inhibition of DNA methyltransferase results in tumor growth inhibition or tumor regression," notes Lonnie Moulder, executive vice president of MGI PHARMA. "Targeting the re-expression of silenced tumor suppressor genes at the molecular level is considered one of the most exciting new approaches for cancer therapeutics. This new patent will provide important intellectual property protection for our work in this field."

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MGI PHARMA is developing MG98 for the purpose of blocking production or the nuclear enzyme DNA methyltransferase. Preventing DNA methyltransferase production allows tumor suppressor genes that have been silenced by methylation, to be re-activated. MG98 has already demonstrated anti-cancer activity in Phase 1 trials. MGI also initiated a Phase 2 trial of MG98 in head and neck cancer patients, and intends to further evaluate MG98 in other cancers where silencing of tumor suppressor genes by DNA methyltransferase has been documented. In preclinical models, MG98 used alone and in combination with other anti-cancer agents has caused shrinkage or inhibited growth of human tumors.

Along with MG98, MGI PHARMA licensed a complementary small molecule DNA methyltransferase inhibitor program that shares the same goal of preventing methylation and silencing tumor suppressor genes. However, the small molecules are being screened for their potential no bind to DNA methyltransferase and block its activity, rather than prevent its production.

The inventor of this patent is Dr. Moshe Szyf, assistant professor of Pharmacology and Therapeutics at McGill university. MethylGene is the exclusive. worldwide assignee of the patent.

About MethylGene

MethylGene Inc. is a privately held, Canadian biopharmaceutical and chemistry-driven rational drug design company focused on the inhibition of enzyme targets associated with disease. MethylGene combines functional genomic technologies with the application of mechanism-based small molecules and mRNA inhibitors to discover, patent, develop and commercialize novel therapeutics for cancer and infectious disease. MethylGene's lead compound, MG98, which is partnered for North America with MGI PHARMA, is currently in Phase 2 clinical trials. The Company has other research and development programs to develop small molecule inhibitors of DNA methyltransferases, histone deacetylases, beta-lactamases and other enzyme targets.

About MGI PHARMA

MGI PHARMA, INC. is an oncology-focused pharmaceutical company that acquires, develops and commercializes proprietary products that meet patient needs and build shareholder value. MGI focuses its sales efforts solely in the United States and

collaborates with other pharmaceutical or biotechnology companies for its products in international markets. For more information about MGI, please visit the company's web site at www.mgipharma.com.

This news release contains forward-looking statements that may include statements regarding intent, belief or current expectations of the Company and its management. These forward-looking statements are not guarantees of future performance and involve a number of risks and uncertainties that may cause the Company's actual results to differ materially from the results discussed in these statements. Factors that might affect MGI PHARMA's results include, but are not limited to the ability of MGI PHARMA's product candidates to be proven safe and effective in humans and to ultimately compete successfully with

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other therapies, continued sales of MGI PHARMA's marketed products, development or acquisition of additional products, reliance on contract manufacturing, changes in strategic alliances, continued access to capital and other risks and uncertainties detailed from time to time in the company's filings with the Securities and Exchange Commission. MGI PHARMA does not intend to update any of the forward-looking statements after the date of this news release to conform then to actual results.

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END PRIVACY ENHANCED MESSAGE

HELSINN

October 3rd, 2001

HELSINN HEALTHCARE ANNOUNCE THE COMPLETION OF PATIENT ENROLLMENT FOR FIRST PALONOSETRON PHASE 3 PIVOTAL TRIAL

HELSINN HEALTHCARE SA announced the completion of patient enrollment for the first of the pivotal Phase 3 trials of palenosetron, a novel 5-HT, antagonist. Palonosetron is a potent, highly selective 5-HT, antagonist with an extended half-fife, currently In Phase 3 development in the United States and Europe for the prevention of chemotherapy-induced nausea and vomiting (CINV). HELSINN expects to complete patient enrollment for the remaining trials in the Phase 3 program near the end of 2001 and plans to submit a New Drug Application (NDA) in the U.S. and Europe in the first half of 2002.

The double-blinded, randomized Phase 3 clinical trial program aims to compare intravenous (IV) palonosetron to currently marketed 5-HT, antagonists arid is being conducted at medical centers across North America and Europe. It is expected that over 1,800 cancer patients receiving either highly- or moderately emetogenic chemotherapy will be enrolled in the trials. Based on the extended half-life of patonosetron and the results of a Phase 2 trial, its efficacy is being assessed over Day 2 through Day 5 following treatment, in addition to the primary efficacy measure of complete response during the 24-hour period after the start of chemotherapy.

Results of Phase 1 trials in healthy volunteers to assess the pharmacokinetic properties and safety of palonosetron were presented at this year's American

Society of Clinical Oncologists (ASCO) meeting in May 2001. Palonosetron was found to have a plasma elimination half-life of 37 hours, which is at least three times longer than marketed agents in its class. This extended half-life of palonosetron and the results of Phase 2 trials assessing the efficacy beyond 24 hours differentiate palonosetron from the currently marketed 5-HT, antagonists indicated for CINV.

Having been studied in more than 1,000 subjects In Phase 1 and Phase 2 trials. palonosetron was well tolerated and had no unexpected or serious adverse reactions. The most frequent adverse events associated with palonosetron are similar to those seen with other 5-HT, antagonists and include headache and constipation, which are generally mild to moderate.

CINV is estimated to occur in approximately 85 percent of cancer patients undergoing chemotherapy and can result in delay or even discontinuation of treatment The advent of 5-HT, antagonists has revolutionized the management of nausea and vomiting experienced by cancer patients undergoing chemotherapy.

HELSINN is the worldwide licensor of palonosetron and is conducting the Phase 3 trials of palonosetron that will form the basis for its registration in the United States. In April of this year, MGI PHARMA, an oncology-focused pharmaceutical company based in Minneapolis, and HELSINN signed an agreement granting MG% the exclusive U.S. and Canadian licensing and distribution rights to palonosetron. Once approved, palonosetron will compete in the CINV treatment market, which is rapidly approaching $1 billion in North America.

HELSINN's negotiations with potential European licensing partners are ongoing, and out-licensing activities for remaining markets will commence next year.

HELSINN

January 16, 2002

HELSINN & MGI PHARMA ANNOUNCE COMPLETION OF PIVOTAL PHASE 3 TRIALS OF PALONOSETRON

LUGANO, SWITZERLAND, and MINNEAPOLIS USA January 16, 2002 – HELSINN HEALTHCARE SA, a privately owned Swiss pharmaceutical group, and MGI PHARMA, INC., (Nasdaq: MOGN) an oncology-focused pharmaceutical company based in Minneapolis, today announced that patient treatment is completed and the data analysis is underway for the pivotal Phase 3 trials of their investigational agent. Palonosetron. Palonosetron is a potent, highly selective 5-HT, receptor antagonist in development in North America and Europe for the prevention of chemotherapy-induced nausea and vomiting (CINV). Submission of the New Drug Application (NDA) for Palonosetron is now planned to occur in the third quarter of 2002.

The Phase 3 clinical trial program was initiated in April 2000 and was designed to compare intravenous (IV) Palonosetron to currently marketed 5-HT, antagonists. The trials were conducted at more than 130 medical centers across North America and Europe, with more than 1,800 cancer patients receiving either highly- or moderately-emetogenic chemotherapy. Based on the extended half-life of Palonosetron and the results of a Phase 2 trial, the efficacy of Palonosetron in the Phase 3 trial is being assessed over Day 2 through Day 5 following treatment, in addition to the primary efficacy measure of complete response during the 24-hour period after the start of chemotherapy.

"We are pleased to have completed all patient treatment and to have begun analysis of the data collected in the Palonosetron Phase 3 clinical program," said Luigi Baroni, senior director of Scientific Affairs Division at HELSINN. "The Phase 2 clinical trial results were promising, and we are hopeful that the Phase 3 Palonosetron data will demonstrate that it can make a difference for cancer patients suffering from CINV."

The half-life of other available 5-HT, receptor antagonists ranges from approximately five to nine hours, whereas Palonosetron has a plasma elimination half-life of nearly 40 hours," notes Dr. John MacDonald, senior vice president of Research and Development at MGI. "The activity seen with Palonosetron in the Phase 2 trial, coupled with its safety profile observed to date, led to the initiation of a Phase 3 program to assess the ability of the drug to provide prolonged protection against CINV with a single dose."

August Consulting

515 Capital of Texas Highway
Suite 150
Austin, Texas 78746
Tel: 512.347.1755
Fax: 512.347.9375

February 7, 2002

Dr. Victor Razckowski, MD, Acting Director

Division of Gastrointestinal and Coagulation Drug Products

HFD-180

Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: Palonosetron HCl IND 39,797 Amendment #140
Request for Pre-NDA Meeting
Sponsor: Helsinn Healthcare SA

Dear Dr. Razckowski:

In accordance with 21 CFR, 312.47 (b) (2), a pre-NDA meeting is requested in preparation for the palonosetron NDA. All phase 3 efficacy trials - PALO-99-03 and PALO-99-04 involving moderately emelogenic CINV and PALO-99-05 involving highly emelogenic CINV - have completed enrollment and preliminary efficacy data are available.

Consistent with your letter of October 10, 2001, please find attached at Appendix #1 preliminary efficacy data for PALO-99-03. In this study, the preliminary data for Complete Response, which is the primary efficacy outcome measure for acute CINV, was 81.0% (153/189) for palonosetron 0.25 mg,

73.5% (139/189) for palonosetron 0.75 mg, and 68.6% (127/185) for ondausetron 32 mg, Preliminary efficacy results for PALO-99- 04 will he included in the background information package projected to be submitted four weeks prior to the meeting, and preliminary efficacy data for PALO-99-05 will be presented at the meeting.

The following information is provided to you regarding the requested meeting:

1. Product name and application number: Palonosetron HCI Intravenous Injection, 0.25 mg (0.05 mg/mL), or 0.75 mg (0.15 mg/mL). Please note that one of these product strengths will be selected for marketing approval based on the phase 3 efficacy data. The NDA number is 21-372.

2. Proposed Indication: "Palonosetron HCI is indicated for the prevention of nausea and vomiting associated with initial and repeated courses of emetogenic cancer chemotherapy, including highly emetogenic chemotherapy."

3. Type of meeting requested: Type B.

4. Brief statement of the purpose of the meeting: The purpose of the meeting is to uncover any unresolved problems regarding overall programs supporting the planned NDA, to review and discuss the planned ISS and ISE analysis and the planned format and content of the ISS and ISE, to discuss the status of the pediatric safety and effectiveness trial and plans to submit these data to review and discuss the proposed labeling, to discuss the proposed approach to the presentation and formatting of data in the NDA and to discuss administrative matters associated with the planned NDA.

5. List of specific objectives/outcomes expected from the meeting.

a. Reach agreement with FDA regarding the typo of NDA submission: 505b1 submitted in hard copy in traditional format (non CID) with CRTs and possibly CRFs submitted electronically on CD.

b. Present PALO-99-05 preliminary efficacy results, review preliminary results for all pivotal clinical efficacy trials and reach agreement on any matters identified by FDA.

c. Review proposed ISS and ISE information to be submitted in the background package and reach agreement on the content and format of the ISS and ISE

d. Discuss the pediatric clinical safety, efficacy and pharmacokinetic study to be submitted, discuss the regulatory approach and schedule to submit these data, and obtain FDA's feedback regarding the acceptability of this approach.

e. Review and discuss the pharrn/tox program, in particular the carcinogenicity and preclinical cardiovascular safety data, and obtain FDA's feedback regarding these data for the planned NDA. f. Briefly

f. Review the biopharm program planned for the NDA and address any outstanding matters identified by FDA.

g. Briefly review the CMC program and address any outstanding matters identified by FDA.

h. Review proposed draft labeling and obtain FDA's feedback.

i. Review proposed content and format for the NDA and obtain FDA's feedback.

j. Review administrative items planned for the NDA.

k. Present and discuss the planned NDA submission schedule.

6. Preliminary proposed agenda and specific questions for purposes of supporting an NDA submission for Palonosetron HCI for Injection.

a. Introductions, including a request for FDA minutes and list of meeting attendees. (5 minutes)

b. Discussion of the proposed NDA submission route and nature of the submission. Please advise us if you agree with the proposed type of NDA submission: 505b1 submitted in hard copy in traditional format (non CTD) with CRTs and possibly CRFs submitted electronically on CD, and discuss as needed. Please advise us of any electronic data you wish to be submitted in the NDA. (5 minutes)

c. Presentation of preliminary PALO-99-05 phase 3 pivotal efficacy results and overall preliminary efficacy results for all phase 3 pivotal efficacy trials. Please advise us of the acceptability of these preliminary pivotal efficacy data for purposes of NDA submission, comment and discuss as needed. (30 minutes)

d. Discussion of the ISS and LSE. Information regarding the ISS and ISE analyses will be provided in the background pre-meeting document. Please advise us of the acceptability of the proposed content and format of the planned ISS and ISE, comment and discuss as needed. (30 minutes)

e. Discussion of plans to submit the PALO-99-07 pediatric clinical trial. A proposed plan to submit a pediatric assessment for the NDA based on pediatric

safety, efficacy and pharmacokinetic study PALO-99-07 will be included in the background package. PALO-99-07 is not projected to be completed until after NDA submission. Please advise us if you agree with the proposed plan to submit the pediatric clinical study, comment and discuss as needed. (5 minutes)

f. Discussion of the pharm/tox program. A brief tabular summary of key studies in the pharm/tox program arid status will be presented in the background package. Please advise us regarding the acceptability of the overall program for purposes of NDA submission, provide commentary and discuss as needed. (30 minutes)

g. Discussion of the CMC program. A brief overview of the CMC program, consistent with the CMC program presented and agreed upon at the FDA meeting held January 31, 2002, will be provided in the background package. Please advise us if you agree with the CMC program for purposes of the planned NDA submission, provide commentary and discuss as needed. (10 minutes)

h. Discussion of the biopharm program. A brief tabular overview of the biopharm program and status will be included in the background package. Please advise us if you agree with the program for purposes of the planned NDA submission, comment and discuss as needed. (10 minutes).

i. Discussion of draft labeling. Proposed draft labeling will be included in the background package. Please advise us if you agree with the proposed draft labeling for purposes of the planned NDA submission, comment and discuss as needed. (25 minutes)

j. Discussion of the content and format of the NDA. The proposed NDA index, outlining sections and

subsections to be included in the NDA, will be provided in the background package. Please advise us if you agree with the proposed content and format for the NDA, comment and discuss as needed. (15 minutes)

k. Discussion of administrative items in the NDA. Please review the proposed NDA index to be included in the background package and advise us if you agree with the proposed administrative items planned for inclusion in the NDA such as user's fee forms, debarment certification, financial information, field copy certification, etc., - we do not wish to miss anything - and discuss as needed. (10 minutes)

l. Discussion of the NDA submission schedule. Please comment and discuss as needed regarding the proposed NDA submission schedule. (2 minutes)

m. Summary comments by the FDA Division Acting Director, Dr. Raczkowski. (3 minutes)

n. Meeting adjourns.

7. Planned Sponsor's attendees:

a. Dr. Dario Ceriani, Senior Manager Regulatory Affairs, Helsinn.

b. Dr. Luigi, Baroni, Direclor of Scientific Affairs, Helsinn.

c. Dr. Giorgio Calderari, Chief Manufacturing Officer , Helsinn. Dr. Claudio Berettera, Project Leader, Helsinn.

e. Dr. Alberto Macciocchi, Deputy Director, Clinical Affairs, Helsinn.

f. Dr. Cecilia Moresino, Statistician, Helsinn.

g. Dr. Sergio Cantoreggi, Manager, Preclinical Development, Helsinn.

h. Dr. Simona Parisi, Manager, Product Development. Helsinn.

i. Dr. Kristen Pluharty, Clinical Pharmacology Consultant.

j. Dr. Mike Thom, Biostatistics Consultant

k. Dr. Steven Grunberg, Clinical Oncology Consultant.

l. Ms. Susan Skinner, CMC Consultant.

m. Dr. Robert Wolters, CMC Consultant

n. Dr. Craig Lehmann, Regulatory Consultant.

8. Requested FDA attendees:

a. Dr. Raczkowski, Acting Director, DGCDP.

b. Dr. Gallo-Tones, Medical Team Leader, DGCDP.

c. Dr. Robert Prizont, Medical Officer, DGCDP.

d. Dr. Tom Permutt, Statistics Team Leader, DGCDP.

e. Mr. Ed Nevius, Supervisor, Mathematical Statistics, DOBII.

f. Dr. Jasti Choudary, Pharm/Tox Team Leader, DOCDP.

g. Dr. Yash Chopra, Pharmacology Reviewer, DGCDP.

h. Dr. Liang Zhou, Chemistry Team Leader, DGCDP.

i. Dr. Joe Sieczkowski. Chemistry Reviewer, DGCDP.

j. Dr. Saresh Doddapaneni, Senior Staff Fellow, Biopharrn,DPEII.

k. Mr. Brian Strongin, Regulatory Health Project Manager, DGCDP.

9. Information Package Submission Date. It is projected that the information package including agenda and final specific questions will be submitted four weeks prior to the scheduled date for the Pre-NDA meeting.

10. Suggested Dates and Times for the Pre-NDA Meeting: The week April 8th to April 12th, 2002, in the morning or afternoon is proposed for the meeting. We request a 3-hour meeting.

I will call Mr. Brian Strongin of your Division for purposes of arranging the meeting. Please call me at 512-347-1755, fax 512-347-9375, if you wish further information.

Best Regards,

/s/ Craig Lehmann
Craig Lehmann, Pharm.D.
Authorized Representative for the IND

Submitted: original plus two copies

Appendix #1 — Preliminary efficacy data for pivotal phase 3 efficacy trial PALO-99-03

Cy: Dr. Dario Ceriani, Senior Manager Regulatory Affairs (Helsinn Healthcare SA)

Mr. Franco DeVecchi Sr., Authorized US Corporate Representative (VPCI Inc.)

AMENDMENT No.1
TO THE SUPPLY AND PURCHASE AGREEMENT

This Amendment No. 1 ("Amendment") to the License Agreement is made and effective as of this 16 day of November, 2003 between HELSINN BIREX PHARMACEUTICALS Ltd., a corporation organized and existing under the laws of Ireland and having its registered office at Damastown, Mulhuddart, Dublin 15, Republic of Ireland (hereinafter called "HBP"), of the one part, and MGI PHARMA, INC., a corporation organized and existing under the law of the state of Minnesota, United States of America and having its registered office at 5775 West Old Shakopee Road, Suite 100, Bloomington, MN 55437-3174, USA (hereinafter called "MGI") of the other part.

WHEREAS, MGI and HBP's Affiliate Helsinn Healthcare SA ("HHC") entered on 6 April 2001 into a License Agreement granting MGI an exclusive, royalty-bearing license under the Patents and to use the Know-how, to distribute, promote, market and sell the Products in the Territory;

WHEREAS, HBP and MGI entered on 6 April 2001 into a Supply and Purchase Agreement (hereinafter referred to as "Agreement") relevant to the supply of the Products from HBP to MGI;

WHEREAS, as a result of Amendment No. 2 to the License Agreement, entered into between MGI and HHC on November 14, 2003 it is now necessary to update and amend the Agreement as described below;

WHEREAS, all capitalized terms used herein shall have the same meaning as set forth in the Agreement unless otherwise indicated.

NOW, THEREFORE, in consideration of the mutual covenants and conditions hereinafter set forth, the Parties agree as follows:

1. With effect from the date hereof, the definition of "Products" included in Article 1.9 of the Agreement shall be entirely replaced by the following new definition:

   "1.12 "Products" means the pharmaceutical preparations for human use (i) in IV dosage form for use in CINV. (ii) in IV dosage form for use in PONV. (iii) in oral dosage form, containing the Compound as an active ingredient in the formulations described in one or more Registrations and such other formulations or uses for which MGI exercises its right of first refusal pursuant to Article 2.6 of the License Agreement. The IV formulation of the Product for CINV, as approved by the U.S. Food and Drug Administration as NDA 21-372 and submitted to the Therapeutic Products Programme of Canada in the IND 9427-H0836-21C, is described in the First Appendix hereto."

2. The floor price of USD 28.50 (US Dollars twenty-eight and fifty cents) per vial, indicated in paragraph 1 of the Second Appendix to the Agreement, shall have to be interpreted and construed as referring exclusively to the IV dosage form (per vial) and oral dosage form (per tablet) for CINV. The floor price per vial for the IV dosage form for PONV destined for the market of the United States of America shall be USD 8.20 (US Dollars eight and twenty cents).

3. Subject to paragraph 2 above, any and all provisions of paragraphs 1, 2 and 3 of the Second Appendix to the Agreement, including but not limited to the supply of free goods provided at paragraph 3 of said Appendix, shall be fully applicable also with regard to each of the IV dosage form for PONV and to the oral form of the Products.

4. Upon execution of this Amendment, the Agreement shall be applicable, mutatis mutandis, also to the IV dosage form for PONV and to the oral dosage form of the Products, except as otherwise expressly provided or limited through specific provisions in this Amendment.

5. MGI's address for the purposes of notices under this Amendment and the Agreement shall be as set forth above.

6. In the case of any conflict between this Amendment and the Agreement, the terms of this Amendment shall prevail. Except as amended hereby, the Agreement shall continue in full force and effect.

IN WITNESS WHEREOF, the Parties hereto have causes this Amendment to be executed in duplicate by their duly authorized officers.

For and on behalf of
HELSINN BIREX PHARMACEUTICALS Ltd.

/s/_____
Enrico Braglia
Managing Director

/s/_____
Riccardo Braglia
Managing Director

For and on behalf of
MGI PHARMA INC.

/s/ Leon O. Moulder Jr.
Leon O. Moulder Jr.
President & CEO

/s/ William C. Brown
William C. Brown
Executive Vice President & CFO

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF:

CALDERARI, ET AL.

Filing Date: July 21, 2005

Art Unit: 1614

Serial No.: 11/186,311

Examiner: Gembeh, Shirley V.

Title: LIQUID PHARMACEUTICAL FORMULATIONS OF PALONOSETRON

STATUTORY DECLARATION OF GIORGIO CALDERARI, DANIELE BONADEO, ROBERTA CANNELLA, ENRICO BRAGLIA, AND RICCARDO BRAGLIA

37 C.F.R. §§ 131 and 132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Giorgio Calderari, Daniele Bonadeo, Roberta Cannella, Enrico Braglia and Riccardo Braglia, hereby give this declaration under 37 C.F.R. §§ 131 and 132:

1) Our names are Giorgio Calderari, Daniele Bonadeo, Roberta Cannella, Enrico Braglia and Riccardo Braglia.

2) With the exception of Enrico Braglia, we are all employed by Helsinn Healthcare SA ("Helsinn"), the assignee of the above-referenced patent application.

3) Enrico Braglia was employed by Helsinn at all times during the events described in this declaration, and left Helsinn in January 2007.

4) We are all inventors for this application. Enrico Braglia and Riccardo Braglia are also inventors of the subject matter described and claimed in WO 2004/045615 to Macciocchi, et al. (the "Macciocchi application"), and WO 2004/073714 to Baroni et al. (the "Baroni application").

5) This patent application is based on the discovery of liquid formulations of palonosetron with improved stability.

6) The formulations can be stored for prolonged periods of time in a variety of conditions without significant degradation or loss of potency, and thus are considered pharmaceutically stable.

7) The formulations were developed by us at Helsinn in the late 1990s, and were completed sometime before March 24, 1999.

8) We filed U.S.S.N. 60/444,351, which was our first patent application based on these formulations, on January 30, 2003.

9) We filed PCT application No. PCT/EP04/000888, claiming priority to the '351 application, on January 30, 2004.

10) We filed U.S.S.N. 11/186,311, claiming priority to the US '351 and PCT '888 applications, on July 21, 2005.

11) Finally, we filed three continuation applications – U.S.S.N. 11/388,268 (the '268 application), U.S.S.N. 11/388,269 (the '269 application), and U.S.S.N. 11/388,270 (the '270 application), claiming priority to the US '311 application, the US '351 application, and the PCT '888 application, on March 4, 2006.

12) Each of the foregoing applications contains the following example of an injectable Formulation of palonosetron hydrochloride:

EXAMPLE 4: FORMULATION I

Ingredient	mg/mL
Palonosetron Hydrochloride	0.05
Mannitol	41.5
EDTA	0.5
Trisodium citrate	3.7
WFJ	10.
Citric acid	1.56
Sodium hydroxide solution and/or hydrochloric acid solution	pH 5.0 ± 0.5

13) For ease of reference, we will refer to this formulation as the Example 4 formulation.

14) The Example 4 formulation was developed by us sometime before March 24, 1999, and transmitted to a

contract manufacturer for Helsinn, Oread Laboratories in Palo Alto California ("Oread"), for the production of commercial scale batches of palonosetron hydrochloride.

15) A copy of the master batch record developed by Oread for the formulation is contained in Exhibit A hereto.

16) The master batch record describes the Example 4 formulation on page 2 of 22.

17) As can be seen, the batch record has an effective date of March 24, 1999, and thus makes clear that we had developed the formulation before this date.

18) In fact, we had invented and were in possession of all of the subject matter currently claimed in U.S.S.N. 111186,311, U.S.S.N. 11/388,268, U.S.S.N. 111388,269, and U.S.S.N. 11/388,270 as of March 24, 1999, *because* we had completed stability studies for the Example .4 formulation, and understood the effect that variations in palonosetron concentration, pH, and excipient concentrations would have on the stability of the formulation.

19) Copies of the claims currently pending in U.S.S.N. 11/186,311, U.S.S.N. 11/388,268, U.S.S.N. 11/388,269, and U.S.S.N. 11/388,270 are attached as Exhibits B, C, D and E, respectively.

20) We are familiar with the work of Macciocchi et al. that is described in WO 2004/045615 (the "Macciocchi application"), and the work of Baroni et al. that is described in WO 2004/073714 (the "Baron' application").

21) In fact, declarants Enrico Braglia and Riccardo Braglia arc both named inventors of the subject matter

described and claimed in the Macciocchi and Baroni applications.

22) With the exception of Dr. Macciocchi, who recently passed away, the inventors for those patent applications are close colleagues of ours who also work at Helsinn or, in the case of Dr. Baroni, recently retired from Helsinn.

23) The Macciocchi and Baroni POT applications were filed on November 6, 2003 and February 18, 2004, respectively, which is more than four years after we first invented the Example 4 formulation, and the formulations described in U.S.S.N. 11/186,311, U.S.S.N. 11/388,268, U.S.S.N. 11/388,269, and U.S.S.N. 11/388,270.

24) At least some of the clinical studies described in the Macciocchi and Baroni applications used the Example 4 formulation.

25) Any description of pharmaceutical formulations of palonosetron described in the Macciocchi and Baroni application was derived entirely from work that we performed leading to the Example 4 formulations, and communicated by us to the inventors for the Macciocchi and Baroni application before November 15, 2002, the priority date for the Macciocchi and Baroni applications.

26) In particular, any description in the Macciocchi and Baroni applications of palonosetron formulations having a pH between 4 and 6, palonosetron concentrations between 0.01 and 2.0 or 5.0 mg/ml, the use of palonosetron hydrochloride, the use of mannitol or a chelating agent in liquid palonosetron formulations, the use of these features in an oral or intravenous formulation, the storage of these formulations for periods exceeding 3 months, 6 months, 1 year, 18

months or 2 years under varying storage conditions including room temperature, was derived entirely from the work we did leading to the Example 4 formulation.

27) All of the formulation development work described in the foregoing paragraphs was performed in Switzerland, which to my knowledge has been a member of the World Trade Organization (WTO) since July 1, 1995, and the United States.

[SIGNATURES ON FOLLOWING PAGE]

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code. I declare under penalty of perjury that the foregoing is true and correct.

/s/ Giorgio Calderari
Giorgio Calderari / Dated: November 21, 2007

s/ Daniele Bonadeo
Daniele Bonadeo Dated: November 21, 2007

/s/ Roberta Cannella
Roberta Cannella Dated: November 21, 2007

/s/ Enrico Braglia
Enrico Braglia Dated: November 21, 2007

/s/ Riccardo Braglia
Riccardo Braglia Dated: November 21, 2007

IN THE UNITED STATES PATENT
AND TRADEMARK OFFICE

IN RE APPLICATION:

MACCIOCCHI, *ET AL.*

Examiner: McMillian, Kara Renita
Serial No. 11/129,839
Art Unit: 1617

Filed: May 16, 2005

Continuation No.: 1648

For Palonosetron for the Treatment of
Chemotherapy Induced Emesis

STATUTORY DECLARATION OF SERGIO CANTOREGGI, ENRICO BRAGLIA, AND RICCARDO BRAGLIA

37 C.F.R. §§ 131

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sergio Cantoreggi, Enrico Braglia and Riccardo Braglia, hereby give this declaration under 37 C.F.R. §§ 131 and 132:

1) Our names arc Sergio Cantoreggi, Enrico Braglia and Riccardo Braglia.

2) We submit this declaration to establish that Alberto Macciocchi, Enrico Braglia, and Riccardo Braglia had conceived the invention defined by claim 1 of this application, and reduced it to practice, before November 16, 2001, the date that Dr. Piraccini published abstract no. 5169 in Blood, vol. 98, no. 11 part 2.

3) In particular, we submit this declaration to establish that Alberta Macciocchi, Enrico Braglia and Riccardo Braglia had conceived the idea to use palonosetron for the treatment of acute and delayed-onset CINV, and had conducted clinical trials in humans to test this idea, at least as early as October 2, 2001.

4) Riccardo Braglia and Sergio Cantoreggi are currently employed by Helsinn Healthcare SA ("Helsinn"), the assignee of the above-referenced patent application. Enrico Braglia no longer works for Helsinn, but was employed by Helsinn at all times during the events described in this declaration.

5) Dr. Alberto Macciocchi is now deceased, but also worked for Helsinn during the events that gave rise to this patent application.

6) Attached hereto in Exhibit A is a portion of the Clinical Study Report for PALO-09-03. This report documents one of the studies that Helsinn sponsored in order to secure FDA's approval to market palonosetron in the United States.

7) As can be seen from page 1 of Exhibit A, Helsinn initiated PALO 99-03 on August 1, 2000, and completed the study on October 2, 2001.

8) As can be seen from page 2, Dr. Alberto Macciocchi was the project manager for PALO-99-03.

9) Enrico Braglia and Riccardo Braglia worked with Dr. Macciocchi as he developed the clinical protocol for PALO-99-03, participated with Dr. Macciocchi in the decision to study palonosetron for the treatment of acute and delayed-onset CINV, and worked with Dr. Macciocchi to fund and implement PALO-99-03.

10) Sergio Cantoreggi has since worked extensively with PALO-99-03, and is very familiar with the work reported in PALO-99-03.

11) We understand that this patent application claims:

> "A method of treating chemotherapy or radiotherapy-induced acute and delayed emesis in an adult human for five days after an emesis inducing chemotherapy or radiotherapy event, comprising administering to said human a single dose of a treatment-effective amount of about 0.25 mg of palonosetron in the form of palonosetron hydrochloride prior to said emesis-inducing event, without administering any further palonosetron during said five day period."

12) Exhibit A proves that we had conceived each of the features of this method, and tested the method in humans, before October 2, 2001.

13) The treatment of acute emesis during day 1 after chemotherapy was the Primary Criterion used to evaluate PALO-99-03, and is described on page 6 of Exhibit A:

> "Complete response (defined as no emetic episode and no rescue medication) during the first 24 hours after administration of chemotherapy."

14) The treatment of delayed emesis during days 2-5 was one of the Secondary Criteria used to evaluate PALO-99-03, and is described on page 6 of Exhibit A:

> "Complete response (no emetic episode and no rescue medication) daily for the 24 to 120 hour interval, for cumulative time periods and for the overall 0 to 120 hour interval, ... number of emetic episodes, time to first emetic episode, ..."

15) The use of a single dose of palonosetron hydrochloride during the five day period, in an amount of 0.25 mg. palonasetron, is described on page 4 of Exhibit A, which refers to Palonosetron HCl as the active ingredient, and the Primary Objective to test "single W doses of palonosetron 0.25 mg."

16) In all of this testing, the palonosetron was administered prior to chemotherapy being initiated.

17) Thus, we had conceived the idea to use 0.25 mg. palonosetron for the treatment of acute and delayed-onset CINV, as described in claim 1, at least as early as August 1, 2001 (the date that the study began).

18) Most important, we had successfully tested the method in human patients, and we had done so before October 2, 2001 (the date the study was completed).

19) As reported on page 8 of Exhibit A,

> "Pairwise testing revealed differences between palonosetron 0.25 mg and ondansetron in favor of palonosetron 0.25 mg. for ... number of emetic episodes on Study Days 1, 2, 3 and the time period 0 to 120 hours ..."

20) The conception and reduction to practice of this invention was performed in, among other countries, Switzerland and the United States.

I declare under penalty of perjury that all statements made herein of my own knowledge are true and that all statements made an information and belief are believed to be true, further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and may jeopardize the validity of this application or any patent issuing thereon.

/s/ Sergio Cantoreggi — Dated: August 23, 2010
Sergio Cantoreggi

/s/ Enrico Braglia — Dated: August 23, 2010
Enrico Braglia

/s/ Riccardo Braglia — Dated: August 23, 2010
Riccardo Braglia

(12) United States Patent Calderari et al.

(10) Patent No.: US 8,598,219 B2

(45) Date of Patent: *Dec. 3, 2013

(54) LIQUID PHARMACEUTICAL FORMULATIONS OF PALONOSETRON

(71) Applicants: Helsinn Healthcare S.A., Lugano (CH); Roche Palo Alto LLC, Palo Alto, CA (US); Simone Macciocchi, Melide (CH); Giulio Macciocchi, Breganzona (CH)

(72) Inventors: Giorgio Calderari, Rancate (CH) Daniele Bonadeo, Casalzuigno (IT); Roberta Cannella, Varese (IT); Alberto Macciocchi, Melide (CH) Andrew Miksztal, Palo Alto, CA (US); Thomas Malefyt, Carmel Valley, CA (US); Kathleen M Lee, Palo Alto, CA (US); Carmine Panuccio. Casnate con Bernat (1T)

(73) Assignees: Helsinn Healthcare SA. Lugano/ Pazzallo (CH); Roche Palo Alto LLC, Palo Alto, CA (US)

(*) Notice: Subject to any disclaimer, the terms of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: 13/901,437

(22) Filed: May 23, 2013

(65) Prior Publication Data

US 2013/0261592 Al Oct. 3, 2013

Related US. Application Data

(63) Continuation-in-part of application No. 13/087,012, filed on Apr. 14, 2011, now Pat. No.

8,518,981, which is a continuation of application No. 11/186,311, filed on Jul. 21, 2005, now Pat. No. 7,947,724, which is a continuation of application No. PCT/EP2004/000888, filed on Jan. 30, 2004.

(60) Provisional application No. 60/444,351, filed on Jan. 30. 2003.

(51) Int. Cl.

A01N 43/52 (2006.01)

(52) U.S. Cl.

USPC 514/397

(58) Field of Classification Search

USPC 514/397

See application file for complete search history.

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Primary Examiner—Shirley Gembeh

(74) *Attorney, Agent. or Firm*—Clark G. Sullivan; Troutman Sanders LLP

(57) ABSTRACT

The present invention relates to shelf-stable liquid formulations of palonosetron for reducing chemotherapy and radiotherapy induced emesis with palonosetron. The formulations are particularly useful in the preparation of intravenous and oral liquid medicaments.

8 Claims, No Drawings

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Defendants Aurobindo Pharma Ltd.'s and Aurobindo Pharma USA Inc.'s Answer, Affimative Defenses, and

Counterclaims, dated Aug. 23, 2013 (D. Del. Case No. 13-688).

Plaintiff's Answer to the Counterclaims of Aurobindo Pharma USA Inc. and Aurobindo Pharma Ltd., dated Sep. 13, 2013 (D. Del. Case No. 13-688).

Aurobindo Pharma Ltd. Paragraph IV notice regarding U.S Patent No. 8,518,981, dated Sep. 19, 2013.

Dr. Reddy's Laboratories, Ltd.'s and Dr. Reddy's Laboratories, Inc.'s Amended Invalidity Contentions Pursuant to L. Pat. R. 3.6(c). dated Jul. 8, 2013 (D.N.J. Case Nos. 11-3962 and 11-5579 consolidated).

Plaintiffs' Responses to Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc.'s Amended Invalidity Contentions, dated Aug. 19, 2013 (D.N.J. Case Nos. 11-3962 and 11-5579; consolidated) (confidentiality designation redacted).

Sandoz Inc.'s Second Amended Invalidity Contentions Pursuant to L. Pat. R. 3.7, dated Jul. 5, 2013 (D.N.J. Case Nos. 11-3962 and 11-5579; consolidated) (confidentiality designation and other portions redacted).

Plaintiffs' Responses to Sandoz Inc.'s Second Amended Invalidity Contentions, dated Aug. 19, 2013 (D.N.J. Case Nos. 11-3962 and 11-5579; consolidated) (confidentiality designation and other portions redacted).

Defendants Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries, Ltd.'s First Amended Invalidity Contentions Pursuant to L. Pat. R. 3.6(c), dated Jul. 5, 2013 (D. N. J. Case Nos. 11-3962 and 11-5579; consolidated) (confidentiality designation redacted).

Plaintiffs' Responses to Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries, Ltd.'s First Amended Invalidity Contentions, dated Aug. 19, 2013 (D.N.J. Case Nos. 11-3962 and 11-5579; consolidated) (confidentiality designation redacted).

Opening Expert Report of Dr. Bert Spilker, dated Sep. 9, 2013 (D.N.J. Case Nos. 11-3962 and 11-5579; consolidated) (confidentiality designation and other portions redacted).

Expert Report of David G. Franc, Pharm.D., dated Sep. 5, 2013 (D.N.J. Case Nos. 11-3962 and 11-5579; consolidated) (confidentiality designation and other portions redacted).

Expert Report of Lee Kirsch, Ph.D., dated Sep. 9, 2013 (D.N.J. Case Nos. 11-3962 and 11-5579; consolidated) (confidentiality designation and other portions redacted).

Expert Report of Patrick P. DeLuca, Ph.D., dated Sep 9, 2013 (D.N J. Case Nos. 11-3962 and 11-5579; consolidated) (confidentiality designation and other portions redacted).

Expect Report of Paul Myrdal, Ph.D., dated Sep. 9, 2013 (D.N.J. Case Nos. 11-3962 and 11-5579; consolidated) (confidentiality designation and other portions redacted).

Complaint for patent infringement filed by Helsinn Healthcare S.A. and Roche Palo Alto LLC against Ben Venue Laboratories, Inc. d/b/a Bedford Laboratories regarding U.S. Patent Nos. 7,947,724, 7,947,725, 7,960,424, and 8,518,981 dated Sep. 25, 2013 (D. Del. Case No. 13-1612).

Complaint for patent infringement filed by Helsinn Healthcare S.A. and Roche Palo Alto LLC against Dr.

Reddy's Laboratories, Ltd., Dr. Reddy's Laboratories, Inc., Sandoz Inc., Teva Pharmaceuticals USA, Inc., and Teva Pharmaceutical Industries, Ltd. regarding U.S. Patent No.8,518,981 dated Sep. 30, 2013 (D.N.J. Case No. (13-5815)),

* cited by examiner

LIQUID PHARMACEUTICAL FORMULATIONS OF PALONOSETRON

FIELD OF THE INVENTION

The present invention relates to shelf-life stable liquid formulations of palonosetron that are especially useful in the preparation of injectable and oral medicaments.

BACKGROUND OF THE INVENTION

Emesis is a devastating consequence of cytotoxic therapy, radiotherapy, and post-operative environments that drastically affects the quality of life of people undergoing such treatments. In recent years a class of drugs referred to as 5-HT_3 (5-hydroxytryptamine) receptor antagonists has been developed that treat such emesis by antagonizing cerebral functions associated with the 5-HT_3 receptor. See *Drugs Acting on 5-Hydroxytryptamine Receptors:* The Lancer Sep. 23, 1989 and references cited therein. Drugs within this class include ondansetron, granisetron, alosetron, tropisetron, and dolasetron. These 5-HT_3 antagonists are often administered intravenously shortly before chemotherapy or radiotherapy is initiated, and can be administered more than once during a cycle of chemotherapy or radiotherapy. In addition, they are often supplied as tablets or oral elixirs to either supplement an intravenous administration, or to ease

home usage of the drug if the patient is self-administering the chemotherapeutic regimen.

Because some chemotherapeutic agents can induce emesis over extended periods of several days even when they are administered only once, it would be desirable to administer an emesis-inhibiting drug such as a 5-HT_3 antagonist every day until the risk of emesis has substantially subsided. The present class of 5-HT_3 antagonists has not proven especially helpful meeting this need, however, because the $5HT_3$ receptor antagonists currently marketed have proven to be less effective in controlling delayed nausea and vomiting than they are at controlling acute emesis. Sabra, K, *Choice of a $5HT_3$ Receptor Antagonist for the Hospital Formulary.* EHP, October 1996: 2 (suppl 1):S19-24.

Recently, clinical investigations have been made concerning palonosetron, a new 5-HT_3 receptor antagonist reported in U.S. Pat. No. 5,202,333. These investigations have shown that the drug is an order of magnitude more potent than most existing 5-HT_3 receptor antagonists, has a surprising half-life of about 40 hours, and is effective to reduce delayed-onset nausea induced by chemotherapeutic agents. However, formulating palonosetron in liquid formulations has not proven an easy task, typically due to shelf-stability issues. U.S. Pat. No. 5,202,333 discloses an intravenous formulation of palonosetron in example 13 that contains the following ingredients:

Ingredient	Mg
Palonosetron HCl	10-100 mg.
Dextrose Monohydrate	q.s. to make Isotonic
Citric Acid Monohydrate	1.05 mg.
Sodium Hydroxide	0.18 mg.
WFI	To 1.0 ml.

The formulation has a pH of 3,7 and a shelf stability of less than the 1-2 year time period required by health authorities in various countries.

Ondansetnon, its uses, and medicaments made with ondansetron are disclosed in U.S. Pat. Nos. 4,695,578, 4,753,789, 4,929,632, 5,240,954, 5,344,658, 5,578,628, 5,578,632, 5,922,749, 5,622,720, 5,955,488, and 6,063,802. Commercially it is distributed by GlaxoSmithKline as Zofran® and is indicated for prevention of postoperative nausea and vomiting (PONV), cancer chemotherapy-induced nausea and vomiting (CINV), and radiotherapy-induced nausea and vomiting (RINV) and it is available as an injection, tablets and solution, and as Zofran ODT® (ondansetron) Orally Disintegrating Tablets.

Granisetron, its uses, and medicaments made with granisetron are disclosed in U.S. Pat. Nos. 4,886,808, 4,937,247, 5,034,398 and 6,294,548. Commercially it is distributed by Roche Laboratories Inc. as Kytril®, indicated for the prevention of nausea and vomiting associated with chemotherapy or radiation therapy, and is offered in tablet form, oral solution, and as an injection.

Alosentron, its uses, and medicaments made with alosetron are disclosed in U.S. Pat. Nos. 5,360,800 and 6,284,770. Commercially it is distributed by GlaxoSmithKline as Lotrunex®.

Tropisetron is commercially available as Navoban® (Novartis) CAS-89565-68-4 (tropisetron); CAS-105826-92-4 (tropisetron hydrochloride) and it is indicated for treatment of PONV and CINV.

Dolasetron, its uses, and medicaments made with ondansetron are disclosed in U.S. Pat. Nos. 5,011,846, and 4,906,755. Commercially it is distributed by Aventis Pharmaceuticals Inc. as Anzemet®, indicated for prevention of both PONV and CINV, and it is offered in the form of a tablet or an intravenous solution.

Therefore, there exists a need for a palonosetron formulation with increased stability and thereby increased shelf life. There also exists a need for an appropriate range of concentrations for both the 5-HT_3 receptor antagonist and its pharmaceutically acceptable carriers that would facilitate making a formulation with this increased stability.

It is an object of the present invention to provide a formulation of Palonosetron hydrochloride with increased pharmaceutical stability for preventing and/or reducing emesis.

It is another object of the invention to provide an acceptable range of concentrations which will stabilize a formulation containing Palonosetron hydrochloride.

It is a further object of the invention to provide a formulation of Palonosetron which would allow for prolonged storage.

It is also an object of the invention to provide a formulation of Palonosetron which would allow terminal sterilization.

SUMMARY OF THE INVENTION

The inventors have made a series of discoveries that support a surprisingly effective and versatile formulation for the treatment and prevention of emesis using palonosetron. These formulations are shelf stable for periods greater than 24 months at mom temperature, and thus can be stored without refrigeration, and manufactured using non-aseptic, terminal sterilization processes.

In one aspect, the inventors have discovered that formulations which include the active ingredient palonosetron require in same instances only 1/10th the amount of other previously known compounds for treating emesis, which surprisingly allows the use of concentrations of palonosetron far below those that would ordinarily be expected. Thus, in one embodiment the invention provides a pharmaceutically stable solution for preventing or reducing emesis comprising a) from about 0.01 mg/mL to about 5 mg/mL palonosetron or a pharmaceutically acceptable salt thereof, and b) a pharmaceutically acceptable carrier.

The inventors have further discovered that by adjusting the formulation's pH and/or excipient concentrations it is possible to increase the stability of palonosetron formulations. Therefore, in another embodiment, the invention provides a pharmaceutically stable solution for preventing or reducing emesis comprising a) palonosetron or a pharmaceutically acceptable salt thereof; and b) a pharmaceutically acceptable carrier, at a pH from about 4.0 to about 6.0. In another embodiment the invention provides a pharmaceutically stable solution for preventing or reducing emesis comprising from about 0.01 to about 5.0 mg/ml palonosetron ore pharmaceutically

acceptable salt thereof; from about 10 to about 100 millimoles citrate buffer; and from about 0.005 to about I.0 mg/ml E respondentDTA.

The inventors have further discovered that the addition of mannitol and a chelating agent can increase the stability of palonosetron formulations. Therefore, in still another embodiment the invention provides a pharmaceutically stable solution for preventing or reducing emetic comprising a) palonosetron or a pharmaceutically acceptable salt thereof and b) a pharmaceutically acceptable carrier, wherein the pharmaceutically acceptable carrier comprises a chelating agent and mannitol,

DETAILED DESCRIPTION OF THE INVENTION

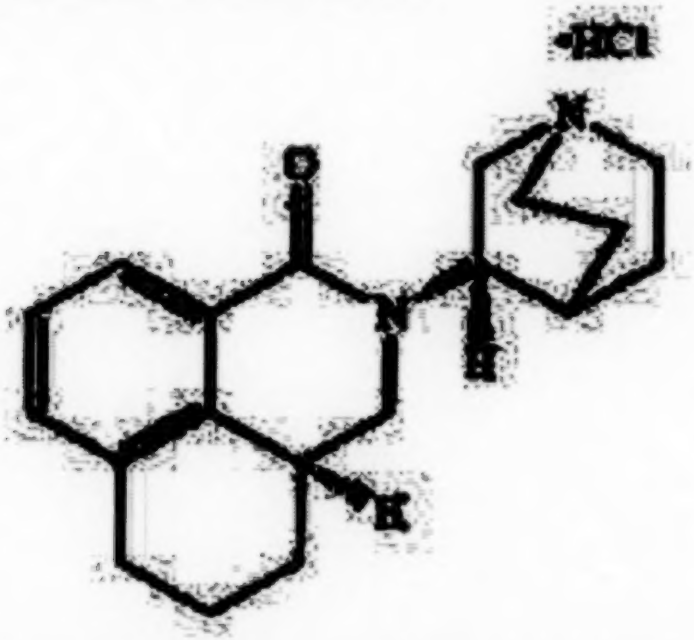
Definitions

"Vial" means a small glass container sealed with the most suitable stopper and seal, other suitable primary containers may be used, for instance, but not limited to, pre-filled syringes. Vial also means a sealed container of medication that is used one time only, and includes breakable and nonbreakable glass vials, breakable plastic vials, miniature screw-top jars, and any other type of container of a size capable of holding only one unit dose of palonosetron (typically about 5 mls.).

Throughout this specification the word "comprise," or variations such as "comprises" or "comprising," will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of' any other element, integer or step, or group of elements, integers or steps

"Palonsetron" means (3aS)-2,3,3a,4,5,6-Hexahydro-2-[(S)-1-Azabicyclo[2.2.2]oct-3-yl]2,3,3a,4,5,6-

hexahydro-1-oxo-[Hbenz[de]isoquinoline, and is preferably present as the monohydrochloride. Palonosetron monohydrochloride can be represented by the following chemical structure:



Concentrations—When concentrations of palonosetron are given herein, the concentration is measured in terms of the weight of the free base. Concentrations of all other ingredients are given based on the weight of ingredient added to the solution.

"Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use.

"Pharmaceutically acceptable salts" means salts which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as acetic acid, propionic acid, hexanoic acid, heptanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, o-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2,-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid p-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, p-toluenesulfonic acid, camphorsulfonicacid, 4-methylbicyclo[2.2.2]oct-2-ene-carboxylic acid, glucoheptonic acid, 4.4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearie acid, muconic acid, and the like.

In addition, pharmaceutically acceptable salts may be formed when an acidic proton present is capable of reacting with inorganic or organic bases. Acceptable inorganic bases include sodium hydroxide, sodium carbonate, potassium hydroxide, aluminum hydroxide and calcium hydroxide. Acceptable organic bases include ethanolamine, diethanolamime, triethanolamine, tromethamine, N-methylglucamine and the like.

Discussion

The fact that palonosetron can be formulated in some instances at concentrations of only about 1/10th the amount of other previously known compounds for treating emesis, surprisingly allows the use of concentrations of palonosetron far below those that would ordinarily be expected. Thus, in one embodiment the invention provides a pharmaceutically stable solution for preventing or reducing emesis comprising a) from about 0.01 mg/mL to about 5 mg/mL palonosetron or a pharmaceutically acceptable sill thereof; and b) a pharmaceutically acceptable carrier. Similarly. in another embodiment the invention provides a method of formulating a pharmaceutically stable solution of palonosetron comprising admixing from about 0.01 mg/mL to about 5 mg/mL palonosetron or a pharmaceutically acceptable salt thereof; with a pharmaceutically acceptable carrier. In alternative embodiments, the formulation includes palonosetron or a pharmaceutically acceptable salt thereof in a concentration from about 0.02 mg/mL to about 1.0 mg/mL, from about 0.03 mg/mL to about 0.2 mg/mL, and most optimally about 0.05 mg/ml.

A particular advantage associated with the lower dosages of intravenous palonosetron is the ability to administer the drug in a single intravenous bolus over a short, discrete time period. This time period generally extends from about 10 to about 60 seconds, or about 10 to about 40 seconds, and most preferably is about 10 to 30 seconds. In one particular embodiment the palonosetron is supplied in vials that comprise 5 ml, of solution, which equates to about 0.25 mg of palonosetron at a concentration of about 0.05 mg/ml.

The inventors have further discovered that by adjusting the formulation's pH and/or excipient concentrations it is possible to increase the stability of palonosetron formulations. Therefore, in another embodiment, the invention provides a pharmaceutically stable solution for preventing or reducing emesis comprising a) palonosetron or a pharmaceutically acceptable salt thereof; and b) a pharmaceutically acceptable carrier, at a pH from about 4.0 to about 6.0. Similarly, in another embodiment the invention provides a method of formulating a pharmaceutically stable solution of palonosetron comprising admixing a) palonosetron or a pharmaceutically acceptable salt thereof; and b) a pharmaceutically acceptable carrier, at a pH from about 4.0 to about 6.0. In alternative embodiments, the pH is from ahem 4.5 to about 5.5, and most optimally about 5.0. There are many examples to those of skill in the art of suitable solutions to adjust the pH of a formulation. Two exemplary solutions are sodium hydroxide and hydrochloric acid solution, either of which could be used to adjust the pH of the formulation,

In another embodiment the invention provides a pharmaceutically stable solution for preventing or reducing emesis comprising from about 0.01 to about 5.0 mg/ml palonosetron or a pharmaceutically acceptable salt thereof and (i) from about 10 to about 100 millimoles citrate buffer, and/or (ii) from about 0.005 to about 1.0 mg/ml EDTA. Similarly, in another embodiment the invention provides a method of formulating a pharmaceutically stable solution of palonosetron comprising admixing from about 0.01 to about 5.0 mg/ml palonosetron or a pharmaceutically acceptable salt thereof and (i) from about 10 to about 100 millimoles citrate buffer, and/or (ii) from about 0.005 to about 1.0 mg/ml EDTA. The citrate buffer can

be in the form of citric acid and/or a salt of citric acid such as trisodium citrate. In various embodiments, the ranges of one or more of the foregoing ingredients can be modified as follows:

The formulation may comprise palonosetron or a pharmaceutically acceptable salt thereof in a concentration from about 0.02 mg/mL to about 1.0 mg/mL, from about 0.03 mg/mL to about 0.2 mg/mL palonosetron hydrochloride, and most optimally about 0.05 mg/ml.

The formulation may comprise citrate buffer in a concentration of from about 10 to about 40 millimoles, or 15-30 millimoles.

The formulation may comprise EDTA in a concentration of from about 0.005 mg/ml to about 1.0 mg/ml, or about 0.3 to about 0.7 mg/ml, and most optimally about 0.5 mg/ml.

The inventors have further discovered that the addition of mannitol and a chelating agent can increase the stability of palonosetron formulations. Therefore, in still another embodiment the invention provides a pharmaceutically stable solution for preventing or reducing emesis comprising a) palonosetron or a pharmaceutically acceptable salt thereof and b) a pharmaceutically acceptable carrier, wherein the pharmaceutically acceptable carrier comprises a chelating agent and mannitol. Similarly, in another embodiment the invention provides a method of formulating a pharmaceutically stable solution of palonosetron comprising admixing a) palonosetron or a pharmaceutically acceptable salt thereof and b) a pharmaceutically acceptable carrier, wherein the pharmaceutically acceptable carrier comprises a chelating agent and mannitol. The chelating agent is

preferably EDTA, and, in various embodiments the chelating agent is present in a concentration of from about 0.005 to about 1.0 mg/mL or from about 0.05 mg/mL to about 1.0 mg/mL or from about 0.3 to about 0.7 mg/ml, or most optimally about 0.5 mg/ml. In various embodiments the mannitol is present in a concentration of from about 10.0 mg/ml to about 80.0 mg/ml, from about 20.0 mg/ml to about 60.0 mg/ml, or from about 40.0 to about 45.0 mg/ml.

Injectable formulations are typically formulated as aqueous solutions in which water is the primary excipient. Oral formulations will differ from injectable formulations generally by the additional presence of flavoring agents, coloring agents, or viscosity agents. Natural or synthetic sweeteners include, among others, mannitol, sorbitol, saccharose, saccharine, aspartame, acelsulphame K. or cyclamate. These agents are generally present in concentrations in excess of 100 mg/ml or 250 mg/ml when used as sweetening agents, in contrast to the 41.5 mg/ml concentration of mannitol described in some of the embodiments of the invention. in which mannitol is acting simply as a tonicifying agent.

The formulations of the present invention are particularly suited for use in injectable and oral liquid formulations, but it will be understood that the solutions may have alternative uses. For example, they may be used as intermediates in the preparation of other pharmaceutical dosage forms. Similarly, they may have other routes of administration including intranasal or inhalation. Injectable formulations may take any route including intramuscular, intravenous or subcutaneous,

Still further embodiments relate to improvements in the ease with which the palonosetron formulation can

be stored or manufactured. In particular, the inventors have discovered that the formulations of the present invention allow storage of the product for extended periods at room temperature. Thus, in yet another embodiment the invention provides a method of storing one or more containers in which are contained a solution of palonosetron or a pharmaceutically acceptable salt thereof comprising: a) providing a room comprising said one or more containers; b) adjusting or maintaining the temperature of the room at greater than about ten, 15, or 20 degrees celcius; and c) storing said containers in said room for one month, 3 months, 6 months, one year, 18 months, 24 months or more (but preferably not exceeding 36 months), wherein (i) the palonosetron or pharmaceutical salt thereof is present in a concentration of from about 0.01 mg/mL to about 5.0 mg/ml, (ii) the pH of the solution is from about 4.0 to about 6.0, (iii) the solution comprises from about 0.01 to about 5.0 mg/ml palonosetron or a pharmaceutically acceptable salt thereof, from about 10 to about 100 millimoles citrate buffer and from about 0.005 to about 1.0 mg/ml EDTA, (iv) the solution comprises a chelating agent, or (v) the solution comprises from about 10 about 100 millimoles of a citrate buffer.

The stability of the foregoing formulations also lends itself well to terminal sterilization processes in the manufacturing process. Therefore, in still another embodiment the invention provides a method of filling a container in which is contained a solution of palonosetron or a pharmaceutically acceptable salt thereof comprising: a) providing one or more sterile open containers (preferably 5 ml. vials) filling said containers with a solution of palonosetron in a non-aseptic environment: c) sealing said filled containers; and d) sterilizing said sealed, filled containers,

wherein (i) the palonosetron or pharmaceutical salt thereof is present in a concentration of from about 0.01 mg/mL to about 5 mg/mL, (ii) the pH of the solution is from about 4.0 to about 6.0. (iii) the solution comprises from about 0.01 to about 5.0 mg/ml palonosetron or a pharmaceutically acceptable salt thereof, from about 10 to about 100 millimoles citrate buffer and from about 0.005 to about 1.0 mg/ml EDTA, (iv) the solution comprises a chelating agent, or (v) the solution comprises from about 10 to about 100 millimoles of a citrate buffer.

EXAMPLES

Example 1

Stabilizing pH

A study was conducted to determine the effect of pH on formulations containing palonosetron hydrochloride, measuring stability at 80° C, at pH 2.0, 5.0, 7.4, and 10.0. The results indicated that palonosetron hydrochloride is most stable at pH 5.0.

Example 2

Stabilizing Concentration Ranges

A formulation optimization study was performed using an experimental design software. Twenty-four lots of drug product were analyzed to investigate the appropriate concentration ranges for palonosetron hydrochloride (0.05 mg/ml to 5.0 mg/ml). citrate buffer (0 to 80 mM) and EDTA (0 to 0.10%). The level of EDTA and citrate buffer were selected based on the optimal formulation, which was shown to be formulated with EDTA 0.05% and 20 mM citrate buffer at pH 5.0. The results of this study indicated that palonosetron concentration was also a critical

factor in chemical stability, with greatest stability seen at the lowest palonosetron concentration.

Example 3

Tonicifying Agent

Formulations of palonosetron hydrochloride in citrate buffer were prepared including either a) sodium chloride or b) mannitol. The palonosetron hydrochloride formulation including mannitol showed superior stability. The optimum level of mannitol required for an isotonic solution was found to be 4.15%.

Example 4

Formulation I

The following is a representative pharmaceutical formulation containing palonosetron that is useful for intravenous formulations, or other liquid formulations of the drug.

Ingredient	mg/mL
Palonosetron Hydrochloride	0.05*
Mannitol	41.5
EDTA	0.5
Trisodium citrate	3.7
Citric acid	1.56
WFJ	q.s. to 1 ml
Sodium hydroxide solution and/or hydrochloric acid solution	pH 5.0 ± 0.5

*calculated as a free base

Example 5

Formulation II

The following is a representative pharmaceutical formulation containing palonosetron that is useful for oral formulations, or other liquid formulations of the drug.

Ingredient	mg/mL
Palonosetron Hydrochloride	0.05*
Mannitol	150
EDTA	0.5
Triaodium citrate	3.7
Citric acid	1.56
WFJ	q.s. to 1 ml
Sodium hydroxide solution and/or hydrochloric acid solution	pH 5.0 = 0.5
Flavoring	q.s.

*calculated as a free base

Example 6

Stability of Palonosetron without Dexamethasone

The physical and chemical stability of palonosetron HCI was studies in concentrations of 5 μg/mL and 30 μg/mL in 5% dextrose injection, 0.9% sodium chloride injection, 5% dextrose in 0.45% sodium chloride injection, and dextrose 5% in lactated Ringer's injection. The admixtures were evaluated over 14 days at 4° C, in the dark and for 48 hours at 23° C, under fluorescent light.

Test samples of palonosetron HCI were prepared in polyvinyl chloride (PVC) bags of the infusion solutions

at concentrations of 5 and 30 μg/mL. Evaluations for physical and chemical stability were performed on samples taken initially and after 1, 3, 5, 7, and 14 days of storage at 4° C, and after 1, 4, 24, and 48 hours at 23° C. Physical stability was assessed using visual observation in normal room light and using a high-intensity monodirectional light beam. In addition, turbidity and particle content were measured electronically. Chemical stability of the drug was evaluated by using a stability-indicating high performance liquid chromatographic (HPLC) analytical technique.

All samples were physically stable throughout the study. The solution remained clear, and little or no change in particulate burden and haze level were found. Additionally, little or no loss of palonosetron HCI occurred in any of the samples at either temperature throughout the entire study period.

Example 7

Stability of Palonosetron with Dexamethasone

The physical and chemical stability of palonosetron 0.25 mg admixed with dexamethasone (as sodium phosphate) 10 mg or 20 mg in 5% dextrose injection or 0.9% sodium chloride injection in polyvinyl chloride (PVC) minibags, and also admixed with dexamethasone (as sodium phosphate) 3.3 mg in 5% dextrose injection or 0.9% sodium chloride injection in polypropylene syringes at 4° C. In the dark for 14 days and at 23° C, exposed to normal laboratory fluorescent light over 48 hours, was studied.

Test samples of palonosetron HCI 5 μg/mL with dexamethasone (as sodium phosphate) 0.2 mg/mL and also 0.4 mg/mL were prepared in polyvinyl chloride (PVC) mini bags of each infusion solution.

Additionally, palonosetron HCI 25 μg/mL with dexamethasone (as sodium phosphate) 0.33 mg/mL in each infusion solution were prepared as 10 mL of test solution in 20-mL polypropylene syringes. Evaluations for physical and chemical stability were performed on samples taken initially and after 1, 3, 7. and 14 days of storage at 4° C. and after 1, 4, 24, and 48 hours at 23° C. Physical stability was assessed using visual observation in normal room light and using a high-intensity monodirectional tight beam. In addition, turbidity and particle content were measured electronically. Chemical stability of the drug was evaluated by using a stability-indicating high performance liquid chromatographic (HPLC) analytical technique.

All samples were physically compatible throughout the study. The solutions remained dear, and little or no change in particulate burden and haze level were found. Additionally, little or no loss of palonosetron HCI and dexamethasone occurred in any of the samples at either temperature throughout the entire study period.

Example 8

Formulation III

The following is a representative pharmaceutical formulation and container closure for palonosetron that is useful for intravenous infusion formulations.

Ingredient	Amount (mg)
Palonosetron Hydrochloride	0.75[a)]
Sodium Chloride	450.0
EOM	225
Sodium citrate	18.5
Citric acid monohydrate	7.8
WFJ	q.s. to 50 mL
Sodium hydroxide solution and/or hydrochloric acid solution	pH 4.8 ± 0.5
Container closure system	plastic container[b)] plus rubber stopper[c)]

[a)] Calculated based on the weight of free base

[b)] Polyethylene multilayer film infusion bag.

[c)] Isoprene rubber stopper

This invention has been described with reference to its preferred embodiments. Variations and modifications of the invention will be obvious to those skilled in the art from the foregoing detailed description of the invention.

What is claimed is:

1. A pharmaceutical single-use, unit-dose formulation for intravenous administration to a human to reduce the likelihood of cancer chemotherapy-induced nausea and vomiting, comprising a 5 mL sterile aqueous isotonic solution, said solution comprising:

palonosetron hydrochloride in an amount of 0.25 mg based on the weight of its free base;

from 0.005 mg/mL to 1.0 mg/mL EDTA; and

from 10 mg/mL to 80 mg/mL mannitol.

wherein said formulation is stable at 24 months when stored at room temperature.

2. The pharmaceutical formulation of claim 1, wherein said EDTA is in an amount of 0.5 mg/mL.

3. The pharmaceutical formulation of claim 1, wherein said mannitol is in an amount of 41.5 mg/mL.

4. The pharmaceutical formulation of claim 1, wherein said solution further comprises a citrate buffer.

5. The pharmaceutical formulation of claim 4 wherein said citrate buffer is at a concentration of 20 millimolar.

6. The pharmaceutical formulation of claim 1, wherein said solution is buffered at a pH of 5.0 ± 0.5.

7. The pharmaceutical formulation of claim 1, wherein said EDTA is in an amount of 0.5 mg/mL, wherein said mannitol is in an amount of 41.5 mg/mL, wherein said solution further comprises a citrate buffer at a concentration of 20 millimolar, and wherein said solution is buffered at a pH of 5.0 ± 0.5.

8. A pharmaceutical single-use, unit-dose formulation for intravenous administration to a human to reduce the likelihood of cancer chemotherapy-induced nausea and vomiting, comprising a 5 mL sterile aqueous isotonic solution, said solution comprising:

palonosetron hydrochloride in an amount of 0.25 mg based on the weight of its free base;

from 0.005 mg/mL to 1.0 mg/mL EDTA; and

from 10 mg/mL to 80 mg/mL mannitol, wherein said formulation is stable at 18 months when stored at room temperature.